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A New Efficient Synthesis of (S)-Dolaphenine ((S)-2-Phenyl-1-(2-thiazolyl)ethylamine), the C-Terminal Unit of Dolastatin 10

Naoko Irako, Yasumasa Hamada,* and Takayuki Shioiri*

Faculty of Pharmaceutical Sciences, Nagoya City University
Tanabe-dori, Mizuho-ku, Nagoya 467, JAPAN

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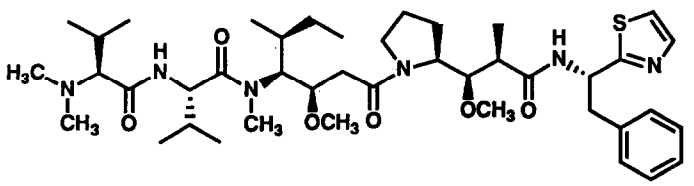
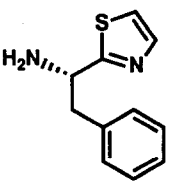
Abstract: Four methods for the preparation of (S)-dolaphenine ((S)-2-phenyl-1-(2-thiazolyl)ethylamine, **2**), which constitutes the C-terminal unit of dolastatin 10 (**1**) having strong anticancer activity, has been investigated. Of these, the most efficient one involved the acylation of 2-lithiothiazole with N-methoxy-N-methylphenylacetamide (**8**), asymmetric reduction with (+)-diisopinocampheylchloroborane (**11g**), followed by the modified Mitsunobu reaction utilizing diphenyl phosphorazidate.

Dolastatin 10 (**1**) has been isolated from an Indian Ocean sea hare *Dolabella auricularia* and has a promising strong anticancer activity.[1] We have already accomplished an efficient stereoselective synthesis of this structurally as well as biologically intriguing molecule.[2,3] This paper deals with the synthetic studies of (S)-dolaphenine ((S)-2-phenyl-1-(2-thiazolyl)ethylamine, **2**), the C-terminal unit of dolastatin 10 (**1**). We have investigated the preparation of **2** as its protected form in four ways. The key steps involve (1) the manganese dioxide oxidation of the thiazolidine, (2) the modified Hantsch thiazole synthesis, (3) the asymmetric reduction of the O-alkyl oximes, and (4) the asymmetric reduction of the ketone followed by the modified Mitsunobu reaction using diphenyl phosphorazidate (DPPA, $(C_6H_5O)_2P(O)N_3$). The last method has been revealed to be the most efficient one among them.



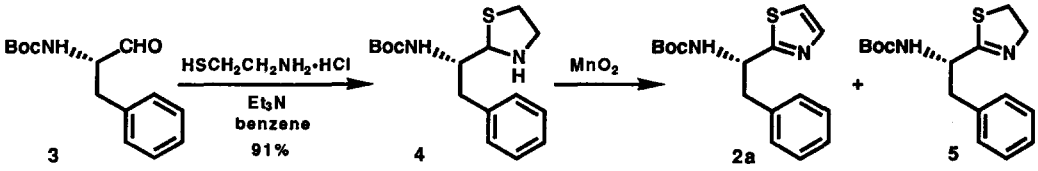
Dolastatin 10 (1)



(S)-Dolaphenine (2)

(1) By the Manganese Dioxide Oxidation

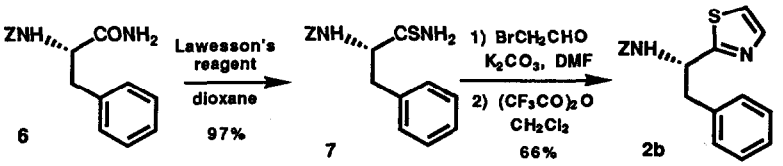
We have already developed[4] a convenient method for the preparation of 2-(1-aminoalkyl)thiazole-4-carboxylic acids by the condensation of N-protected α-amino aldehydes with cysteine followed by the manganese dioxide (MnO_2) oxidation of the resulting thiazolidines. According to this method, tert-butyloxycarbonyl(Boc)-(S)-phenylalaninal (**3**) was condensed with 2-mercapto-ethylamine to give the thiazolidine **4** in excellent yield. Oxidation of **4** with battery grade MnO_2 (chemical manganese dioxide, CMD) by the usual method,[4] however, sluggishly proceeded to give a mixture of Boc-(S)-dolaphenine (**2a**) and the corresponding thiazoline derivative (**5**) in low yields, as shown in Scheme 1. The optical purity of **2a** was determined to be 72% ee by use of chiral HPLC. Pettit and co-workers already reported[3a] the satisfactory preparation of **2a** from **4** utilizing a column of battery grade MnO_2.[5] We also used the column method but failed to produce **2a** in good yield.[6] This unsatisfactory result may be due to the difference of the quality of battery grade MnO_2.



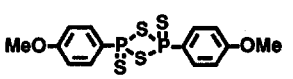
Scheme 1

(2) By the Modified Hantsch Method

Next, the modified Hantsch method developed by Schmidt and co-workers[7] was applied to the preparation of N-benzyloxycarbonyl(Z)-(S)-dolaphenine (**2b**). Thus, Z-(S)-phenylalanine amide (**6**) was first transformed to the corresponding thioamide **7** in almost quantitative yield by use of the Lawesson's reagent. Reaction of **7** with bromoacetaldehyde followed by the dehydration of the resulting 4-hydroxythiazoline with trifluoroacetic anhydride afforded **2b** in good yield, shown in Scheme 2. However, **2b** thus obtained was partially racemized (53% ee). Repeated recrystallizations from hexane-ether afforded optically pure Z-(S)-dolaphenine (**2b**).



Lawesson's reagent:



Scheme 2

Furthermore, racemized Z-dolaphenine (**2b**) was deprotected with hydrogen bromide to give **2**, which was resolved as the salt of (R,R)-tartaric acid. Treatment of the tartrate salt with p-toluenesulfonic acid afforded optically pure (S)-dolaphenine (**2**) as its p-toluenesulfonate salt.

(3) By the Asymmetric Reduction of the O-Alkyl Oximes 10

Although the above Hantsch method provided a required quantity of our synthesis of dolastatin 10 (**1**),[2c] we further explored the more efficient method for the preparation of (S)-dolaphenine (**2**) utilizing the asymmetric reduction method, as shown in Scheme 3. Phenylacetic acid was condensed with N-methoxy-N-methylamine by use of diethyl phosphorocyanidate (DEPC, $(C_2H_5O)_2P(O)CN$) in the presence of triethylamine,[8] giving the amide **8** quantitatively. Reaction of **8** with 2-thiazolyllithium prepared from 2-bromothiazole and butyllithium smoothly afforded benzyl 2-thiazolyl ketone (**9**). Condensation of **9** with methoxyamine and benzyloxyamine gave the O-alkyl oximes **10a** and **10b**, respectively, in excellent yields. Both **10a** and **10b** were revealed to be a mixture of anti and syn isomers. Asymmetric reduction of the O-alkyl oximes **10a** and **10b** was respectively carried out by use of the borane complex of (S)-(-)-2-amino-3-methyl-1,1-diphenylbutanol (Itsuno's reagent, **11a**),[9] followed by conversion to (R)-**2a**, as shown in Scheme 3. Both the yields and enantiomeric excess were not satisfactory, shown in Table 1.

Scheme 3

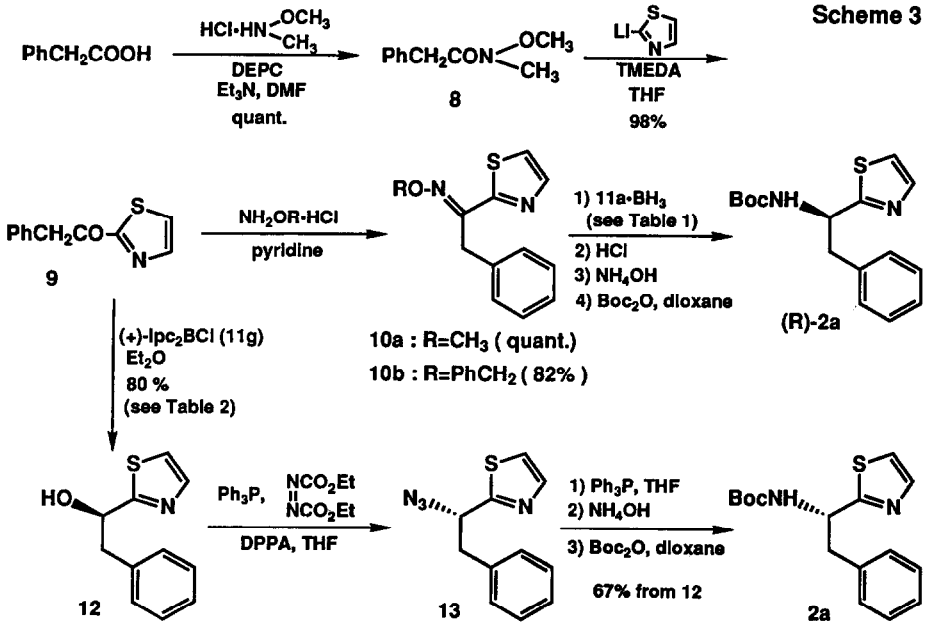


Table 1. Asymmetric Reduction of the O-Alkyl Oximes 10 with 11a•BH_3

Run	R (anti/syn)	Lewis Acid	Reduction Yield(%)	Product 2a ee(%)[a]	Config.[b]	Recovery of 10 (%, anti/syn)
1	CH_3 (4/1)	-	trace	-	-	55 (4/1)
2	CH_3 (4/1)	$AlCl_3$	13	4	R	80 (anti)
3	$PhCH_2$ (5/1)	-	43	54	R	39 (5/1)
4	$PhCH_2$ (5/1)	$AlCl_3$	57	30	R	29 (anti)

a) Determined by ^{1}H-NMR spectral analysis of the corresponding MTPA amide.
b) Configuration of the predominant isomer.

(4) By the Asymmetric Reduction of the Ketone 9

Finally, we extensively investigated the asymmetric reduction of the ketone **9** utilizing chiral boron reagents, as shown in Table 2. So far as tried, use of (-)- and (+)-diisopinocampheylchloroborane (Ipc_2BCl, Brown's reagent, **11f** and **11g**)[10] gave the best results, giving (S)- and (R)-alcohols ((S)- and (R)-**12**), respectively, in good yields and enantiomeric excess (93% ee) (Scheme 3 shows a series of reactions using (+)-Ipc_2BCl). Diethyl ether will be the solvent of choice. The (R)-alcohol, (R)-**12**, smoothly underwent the Mitsunobu reaction by use of a mixture of triphenylphosphine, diethyl azodicarboxylate, and diphenyl phosphorazidate (DPPA, $(C_6H_5O)_2P(O)N_3$),[11,12] giving the (S)-azide **13**, as shown in Scheme 3. Successive treatment of **13** with triphenylphosphine, aqueous ammonia, and di-tert-butyl dicarbonate (Boc_2O) afforded Boc-(S)-dolaphenine (**2a**) in 67% overall yield from the (R)-alcohol, (R)-**12**. Recrystallization from acetone-hexane afforded optically pure **2a**. The overall yields from phenylacetic acid to Boc-dolaphenine (**2a**) were 52.5% in 7 steps.

Thus, we have established a new efficient synthesis of (S)-dolaphenine ((S)-2-phenyl-1-(2-thiazolyl)ethylamine, **2**), the C-terminal unit of dolastatin 10 (**1**), using the asymmetric reduction with (+)-Ipc_2BCl (**11g**), followed by the modified Mitsunobu reaction by use of DPPA. The method developed here will be very useful for the preparation of dolastatin 10, a promising anticancer agent, on a large scale, and can be applied to the synthesis of some other optically active analogs.[13]

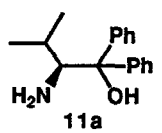
EXPERIMENTAL

Melting points were determined on a YAMATO MP-21 apparatus. Distillation was carried out by a Kugelrohr apparatus. Infrared (IR) spectra were measured with a JASCO IRA-2 or SHIMADZU FT IR-8100 spectrometer. ^{1}H-NMR spectra were recorded on a JEOL PMX-60, FX-100, EX-270, or GSX-400 spectrometer with tetramethylsilane as an internal standard. Optical rotations were measured with a JASCO DIP-140 automatic polarimeter. HPLC was carried out with an Erma Optical Works ERC-8710 or a JASCO Tri Rotar-II high-pressure liquid chromatograph and

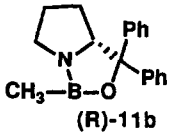
Table 2. Asymmetric Reduction of Benzyl 2-Thiazolyl Ketone (9)

Run	Reducing Agent	Solvent	Reaction Temp.(°C)	Time(h)	Reduction Yield(%)	Product 12 ee(%)[a]	Config.[b]	Recovery of 3 (%)
1	**11a**	THF	-78	2	45	0.9	R	36
2	**11a**	THF	0	0.5	79	30	R	-
3	**11a**	THF	room temp.	0.5	40	40	R	-
4	**11a**	THF	30	10 min	40	53	R	-
5	**11a**	THF	50	5 min	30	45	R	-
6	**11a**[c]	THF	0	20 min	45	13	R	-
7	(R)-**11b**	THF	room temp.	1	20	7	S	10
8	(S)-**11b**	THF	room temp.	15 min	56	10	R	-
9	(S)-**11b**	THF	0	15 min	53	9	R	-
10	(S)-**11b**	THF	-78	0.5	23	0.5	S	2
11	**11c**	THF	room temp.	7 days	0	-	-	88
12	**11d**	THF	-78	3	83	4	S	2
13	**11d**	THF	0	1	66	2	R	33
14	**11e**	THF	-78	3	91	44	S	-
15	**11e**	d	-78	3	85	46	S	-
16	**11f**	THF	-20	4	32	94	S	24
17	**11f**	THF	0	4	74	93	S	-
18	**11f**	THF	room temp.	4	56	90	S	-
19	**11f**	CH_2Cl_2	0	5	69	19	S	17
20	**11f**	benzene	0	8	54	88	S	14
21	**11f**	Et_2O	0	23	75	93	S	-
22	**11f**	Et_2O	room temp.	23	71	81	S	-
23	**11g**	Et_2O	0	23	80	93	R	-

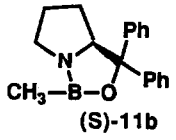
a) Determined by HPLC analysis.
b) Configuration of the predominant isomer.
c) With BF_3·Et_2O.
d) THF/Et_2O/pentane = 4:1:1



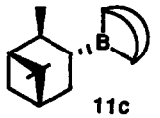
11a



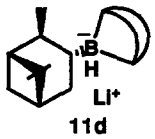
(R)-11b



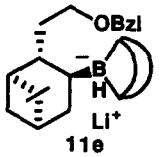
(S)-11b



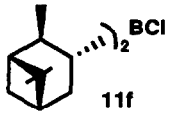
11c



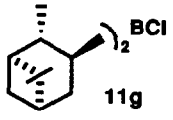
11d



11e



11f



11g

Opti-Pak TA (purchased from Waters Co., Ltd.) was used as a chiral column with isopropanol in hexane as an eluent. Silica gel (BW-820MH or BW-200) was used for column chromatography. Preparative thin layer chromatography (PLC) was carried out on silica gel plates (Merck Art 5744, 0.5 mm thickness). Chemical manganese dioxide (CMD) (I.C. sample No. 12) was purchased from the IBA office (Cleveland, OH 44101). 5,5-Diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (Corey's reagent)[14] was purchased from Tokyo Kasei Co., Ltd. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were dried by distillation from benzophenone ketyl and lithium aluminum hydride, respectively. Other solvents were distilled and stored over molecular sieves (4A).

(1) By the Manganese Dioxide Oxidation

Boc-(S)-Phenylalaninal (Boc-(S)-Phe-al, 3). To a solution of Boc-(S)-phenylalaninol (Boc-(S)-Phe-ol) (25.1 g, 0.10 mol), prepared according to our method,[4] and triethylamine (42 ml, 0.30 mol) in CH_2Cl_2 (300 ml) cooled to -10°C was added in one portion sulfur trioxide-pyridine complex (47.7 g, 0.30 mol) in dimethyl sulfoxide (300 ml). The mixture was stirred vigorously at room temperature for 10 min, poured into ice-saturated aqueous NaCl (900 ml), and extracted with cooled Et_2O (300 ml × 2, 200 ml × 1). The organic extracts were washed with cooled 10% aqueous citric acid (200 ml) and cooled saturated NaCl (200 ml), dried over Na_2SO_4, and concentrated *in vacuo* to give Boc-(S)-Phe-al (**3**) (24.9 g, quant.), which was used for the next step without further purification.

(2RS,1'S)-2-[1'-((tert-Butoxycarbonyl)amino)-2'-phenylethyl]-1,3-thiazolidine (4). To a stirred solution of the crude Boc-(S)-Phe-al (**3**) (12.79 g) in benzene (100 ml) was added 2-mercaptoethylamine hydrochloride (6.82 g, 0.06 mol), and then triethylamine (8.4 ml, 0.06 mol). The mixture was stirred at room temperature for 18.5 h, and diluted with AcOEt (250 ml), washed with saturated aqueous NaCl (100 ml), and dried over Na_2SO_4. Concentration *in vacuo* gave the thiazolidine **4** as colorless crystals (15.83 g, quantitative yield from Boc-Phe-ol), which was used for the next step without further purification. IR (KBr): 3350, 3030, 1710, 1680, 1525, 1170 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.37 (s, 9H), 2.4-3.2 (m, 6H), 3.2-3.7 (m, 1H), 4.6-5.1 (m, 1H), 7.17 (s, 5H).

Manganese Dioxide (CMD) Oxidation of the Thiazolidine 4.

a) By the Ordinary Method.[4] To CMD (445 mg, 4.98 mmol) suspended in dioxane (2 ml) was added the thiazolidine **4** (151 mg, 0.50 mmol) in dioxane (3 ml) at room temperature. The mixture was stirred at 50°C for 62 h. The insoluble materials were removed by filtration and washed with dioxane. The filtrate was concentrated *in vacuo*, and the residue was purified by PLC (20 cm × 20 cm × 3, benzene-Et_2O (6:1)), to give Boc-(S)-dolaphenine (**2a**) (23 mg, 15%) as a pale yellow solid (72% ee, see the physical data below), and (S)-2-[1'-((tert-

butoxycarbonyl)amino)-2'-phenylethyl]-3-thiazoline (**5**) (27 mg, 18%) as a pale yellow solid. IR (nujol): 3250, 1710, 1630, 1520, 1460, 1170 cm.$^{-1}$ ^{1}H-NMR ($CDCl_3$) δ: 1.40 (s, 9H), 3.02 (dd, 1H, J=13.6, 6.2 Hz), 3.20 (dd, 1H, J=13.9, 5.1 Hz), 3.30 (t, 2H, J=8.3 Hz), 4.21 (dt, 2H, J=8.4, 1.5 Hz), 4.79 (brd, 1H, J=5.3 Hz), 5.15 (brd, 1H, J=2.2 Hz), 7.18-7.30 (m, 5H). MS m/z: 306 (M^+).

b) By the Column Method.[5] The thiazolidine **4** (111 mg, 0.36 mmol) in dioxane (2 ml) was applied to a column prepared from a slurry of CMD (3 g, 33.5 mmol) in dioxane, and the column was eluted with dioxane (20 ml) for 2.5 h. The eluate was concentrated *in vacuo*, and the residue was purified by PLC (20 cm × 20 cm × 3, benzene-Et_2O (6:1)) to give **2a** (32 mg, 29%) and **5** (20 mg, 18%).

(2) By the Modified Hantsch Method

Z-(S)-Phenylalanine Thioamide (7). A mixture of Z-(S)-phenylalanine amide (Z-(S)-Phe-NH_2, **6**) (15.6 g, 52 mmol) and the Lawesson's reagent (11 g, 27.2 mmol) in dioxane (80 ml) was heated to 60 °C for 30 min and then stirred at ambient temperature for 8 h. After removal of the volatiles, a mixture of saturated aqueous $NaHCO_3$ and water (1:1, 200 ml) was added and the resulting yellow crystals were collected and washed with water to give **7** (15.9 g, 97%), mp 142-144°C. IR (KBr): 3280, 1690, 1620, 1530, 1240 cm.$^{-1}$ High mass calcd for $C_{17}H_{18}N_2O_2S$: 314.10889. Obsd: 314.10839.

Z-(S)-Dolaphenine (2b). A solution of bromoacetaldehyde in DMF was prepared as follows: diethyl bromoacetal (14.8 ml, 96 mmol) was hydrolyzed with concentrated hydrochloric acid (16.3 ml) between 55 and 60°C for 30 min. The mixture was cooled to about 10°C, and dehydrated with molecular sieves 3A (96 g) in DMF (240 ml). The solution after decantation was used without further purification. The bromoacetaldehyde solution thus prepared was added dropwise to a mixture of Z-(S)-phenylalanine thioamide (**7**) (20.1 g, 64 mmol) and potassium carbonate (44.2 g, 320 mmol) over 10 min and the mixture was stirred at room temperature for 5 h. The mixture was diluted with ethyl acetate and benzene (5:1, 1 L), washed with H_2O (500 ml × 2) and saturated brine, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude thiazoline as a yellow solid which was directly used for the next reaction.

The above material was dissolved in CH_2Cl_2 (150 ml) and cooled to 0-5°C. Trifluoroacetic anhydride (9.04 ml, 64 mmol) was added dropwise and the reaction mixture was stirred at ambient temperature for 1h. After removal of the volatiles *in vacuo*, the residue was dissolved in ether (600 ml), washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated *in vacuo* to afford the crude product, which was chromatographed on silica gel (BW-820MH, 120 g, AcOEt-hexane = 1:4) to give the Z-(S)-dolaphenine (**2b**) (14.3 g, 66%) as a yellow oil which was 53% ee by HPLC analysis using Opti-Pak TA (1% isopropanol in hexane). Recrystallization from Et_2O-hexane (1:1, 150 ml) gave the racemic **2b** (6.95 g) as

colorless prisms, mp 88-91°C. The filtrate was concentrated *in vacuo* and the residue was recrystallized from Et_2O-hexane (1:1, 50 ml) to give the optically pure **2b** (2.05 g) as colorless needles, mp 74-75°C. $[\alpha]^{24}_D$ - 21.9° (c=1.03, MeOH). IR (KBr): 3200, 1710, 1550, 1500, 1250, 1010 $cm.^{-1}$ ^{1}H-NMR ($CDCl_3$) δ: 3.3 (2H, d, J=6.6 Hz), 5.09 (2H, s), 5.37 (1H, dd, J=6.6, 7.9 Hz), 5.58 (1H, d, J=7.9 Hz), 7.05 (1H, d, J=3.3 Hz), 7.19-7.26 (5H, m), 7.32 (5H, S), 7.74 (1H, J=3.3 Hz). High mass calcd for $C_{19}H_{18}N_2O_2S$: 338.10889. Obsd: 338.10902.

(S)-Dolaphenine (R,R)-Tartrate. Z-(S)-Dolaphenine (**2b**) (80% ee, 2.5 g, 7.4 mmol) was treated with 25% HBr-AcOH (25 ml) at 25°C for 2 h and then diluted with dry ether (100 ml). The mixture was decanted and the residue was washed twice with dry ether (50 ml × 2). The resulting yellow crystals were treated with saturated aqueous $NaHCO_3$ (80 ml) and extracted twice with CH_2Cl_2 (80 ml × 2). The organic layer was dried over Na_2SO_4, filtered, and evaporated *in vacuo* to leave the crude dolaphenine (**2**) (1.7 g, quant.) as a brown oil. The crude material was dissolved in EtOH (6 ml) and (R,R)-tartaric acid (1.11 g, 7.4 mmol) was added. The solution was diluted with water (2 ml) to give (S)-dolaphenine (R,R)-tartrate (1.3 g, 50%) as colorless needles which were >96% ee by HPLC analysis, mp 172-176°C.

(S)-Dolaphenine p-Toluenesulfonate. (S)-Dolaphenine (R,R)-tartrate (1.3 g, 3.7 mmol) obtained as above was suspended in a mixture of EtOH (4 ml) and Et_2O (24 ml), and p-TsOH•H_2O (761 mg, 4 mmol) was added. The mixture was stirred at room temperature for 1 h, and filtered to give the p-toluenesulfonate (1.21 g 88%) as colorless crystals, mp 130-133°C, $[\alpha]^{24}_D$ + 28.25° (c 1.04, MeOH). IR (KBr): 3400, 1624, 1498, 1252, 1169, 1122, 1005 cm^{-1}.

Resolution of Racemic Z-Dolaphenine (2b). Racemic Z-dolaphenine (**2b**) (8.4 g, 24.8 mmol) was deprotected as described above. The crude dolaphenine (**2**) was resolved with (R,R)-tartaric acid (3.75 g, 25 mmol), EtOH (12 ml) and H_2O (4 ml). Thus obtained (S)-dolaphenine (R,R)-tartrate (4.9 g, 56%) was 80% ee and recrystallized from EtOH-H_2O (6:1, 14 ml) to give the optically enriched (R,R)-tartrate (3.9 g) with > 91% ee. The combined filtrate was converted to the free amine and precipitated by treatment with (S,S)-tartaric acid (1.9 g, 12.6 mmol), EtOH (9 ml), and H_2O (3 ml) to give the (R)-dolaphenine (S,S)-tartrate (2.0 g, 23%) with 87% ee. Recrystallization from EtOH-H_2O (6:1) produced the optically enriched material. HPLC analysis was carried out after conversion of the dolaphenine salt to the Boc derivative.

(3) By the Asymmetric Reduction of the O-Alkyl Oximes 10

N-Methoxy-N-methylphenylacetamide (8). To a solution of phenylacetic acid (4.1 g, 30 mmol) in DMF (70 ml) was added N,O-dimethylhydroxylamine

hydrochloride (3.23 g, 33.1 mmol). DEPC (4.80 ml, 31.6 mmol) and then triethylamine (TEA) (8.40 ml, 60.3 mmol) were added dropwise to the mixture at -10°C, and the whole was stirred at -10°C for 0.5 h, then at room temperature for 2.5 h. The reaction mixture was dissolved in benzene-AcOEt (1:2) (1 L), and washed with saturated aqueous $NaHCO_3$ (200 ml), water (200 ml), and saturated aqueous NaCl (200 ml), and dried over Na_2SO_4. Concentration *in vacuo* gave the residue, which was purified by silica gel column chromatography to give **8** (5.35 g, 100%) as a pale yellow oil, bp 130°C/0.8 mmHg. IR (film): 1660, 1380, 1010, 730, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.10 (s, 3H), 3.51 (s, 3H), 3.70 (s, 2H), 7.13 (s, 5H). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.23; H, 7.49; N, 7.83.

Benzyl 2-Thiazolyl Ketone (9). To a stirred solution of butyllithium (1.64 M in hexane, 6 ml, 10.0 mmol) and N,N,N',N'-tetramethylethylenediamine (TMEDA) (1.61 ml, 9.99 mmol) in THF (20 ml) at -78°C was added dropwise 2-bromothiazole (0.90 ml, 9.99 mmol), and the reaction mixture was stirred at -78°C for 2 h. Then N-methoxy-N-methylphenylacetamide (**8**) (1.48 g, 8.26 mmol) in THF (20 ml) was added. After being stirred at -78°C for 0.5 h and then at -10°C for 2 h, the reaction mixture was quenched with aqueous $KHSO_4$ (1 M, 50 ml). The whole was extracted with Et_2O (100 ml × 2) and the organic layer was washed with water (70 ml) and saturated aqueous NaCl (70 ml), and dried over Na_2SO_4. Concentration *in vacuo* gave the residue, which was purified by distillation at 150°C/2.5 mmHg to give **9** (1.65 g, 98%), which was crystallized, mp 60-61.5°C (Et_2O-hexane). IR (nujol): 1684, 1377, 723 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.35 (s, 2H), 7.18 (s, 5H), 7.51 (d, 1H, J=3 Hz), 7.90 (d, 1H, J=3 Hz). Anal. Calcd for $C_{11}H_9NOS$: C, 65.00; H, 4.46; N, 6.89. Found: C, 65.21; H, 4.30; N, 6.90.

Benzyl 2-Thiazolyl Ketone O-Methyloxime (10a). To a solution of benzyl 2-thiazolyl ketone (**9**) (124 mg, 0.61 mmol) in pyridine (5 ml) was added portionwise O-methylhydroxylamine hydrochloride (58 mg, 0.69 mmol) and the reaction mixture was stirred at room temperature for 22 h. The solvent was concentrated *in vacuo*, and the residue was diluted with water (20 ml) and extracted with Et_2O (30 ml × 2). The organic layer was washed with saturated aqueous $NaHCO_3$ (20 ml), water (20 ml), and saturated aqueous NaCl (20 ml), and dried over Na_2SO_4. Concentration *in vacuo* gave the residue, which was purified by silica gel column chromatography with hexane-AcOEt (5:1) to give **10a** as a pale yellow oil (142 mg, quantitative), which was a mixture of anti and syn isomers (4:1), bp 150°C/0.7 mmHg. IR (film): 1600, 1490, 1160, 1010, 870, 710, 690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.04 (s, 0.6H), 4.15 (s, 2.4H), 4.24 (s, 1.6H), 4.27 (s, 0.4H), 7.17-7.41 (m, 6.2H), 7.50 (d, 0.8H, J=3.1 Hz), 7.83 (d, 0.2H, J=3.1 Hz), 7.94 (d, 0.8H, J=3.1 Hz). Anal. Calcd for $C_{12}H_{12}N_2OS$: C, 62.05; H, 5.21; N, 12.06. Found: C, 62.20; H, 5.28; N, 11.80.

Benzyl 2-Thiazolyl Ketone O-Benzyloxime (10b). Prepared from benzyl 2-thiazolyl ketone (**9**) (1.02 g, 5.03 mmol), and O-benzyl hydroxylamine hydrochloride (0.89 g, 5.58 mmol) in pyridine (50 ml) as described in the preparation of the O-methyloxime **10a**. Colorless crystals (1.27 g, 82%) of **10b** were a mixture of anti and syn isomers (5:1), mp 45-46°C, bp 180°C/1.05 mmHg. IR (nujol): 1450, 1370, 1055, 690 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 4.23 and 4.29 (2 × s, 2H), 5.26 (s, 0.35H), 5.40 (s, 1.65H), 7.13-7.47 (m, 11H), 7.83 and 7.92 (2 × d, 1H, J=3.3 Hz). Anal. Calcd for $C_{18}H_{16}N_2OS$: C, 70.10; H, 5.23; N, 9.08. Found: C, 70.28; H, 5.18; N, 9.07.

Boc-(R)-Dolaphenine ((R)-2a). To a solution of (S)-(-)-2-amino-3-methyl-1,1-diphenylbutanol (**11a**, 320 mg, 1.25 mmol) in THF (0.5 ml) was added dropwise borane-THF (1M in THF, 2.5 mmol) at 0°C under argon atmosphere. The resulting solution was stirred at 0°C for 8 h.[9] A solution of **10b** (309 mg, 1.00 mmol) in THF (2 ml) was then added dropwise. The resulting mixture was stirred at 30°C for 40 h, and then cooled with ice-water, gradually acidified with 2 M HCl and concentrated *in vacuo*. The residue diluted with water (5 ml) was washed with Et_2O (30 ml × 2). The aqueous layer was cooled with ice-water, basified with 28% aqueous ammonia, and extracted with Et_2O (30 ml × 2). The organic layer was dried over $MgSO_4$. Concentration *in vacuo* gave a white solid (295 mg) which was a mixture of (S)-dolaphenine (**2**) and (S)-(-)-2-amino-3-methyl-1,1-diphenylbutanol (**11a**) The mixture was dissolved in dioxane (2 ml) and Boc_2O (315 mg, 1.44 mmol) in dioxane (2 ml) was added at 0°C. The mixture was stirred at room temperature for 16 h and diluted with water (20 ml). The mixture was extracted with AcOEt (30 ml × 2). The extracts were washed with saturated aqueous NaCl (20 ml) and dried over Na_2SO_4. Concentration *in vacuo* gave the white solid, which was purified by silica gel column chromatography with benzene-Et_2O (6:1) to give Boc-(R)-dolaphenine ((R)-**2a**) (130 mg, 43%, 54% ee) as a white powder.

(4) By the Asymmetric Reduction of the Ketone 9

Asymmetric Reduction of the Ketone 9 with Chiral Reagents.

a) Preparation of Racemic 2-Phenyl-1-(2-thiazolyl)ethanol (rac-12). To a solution of benzyl 2-thiazolyl ketone (**9**) (91 mg, 0.45 mmol) in EtOH (3 ml) at 0°C was added sodium borohydride (30 mg, 0.79 mmol) and the reaction mixture was stirred at 0°C for 1.5 h. The mixture was gradually acidified with 10% aqueous citric acid (1.5 ml), and concentrated *in vacuo*. Water (10 ml) was added to the residue, and the mixture was extracted with Et_2O (30 ml × 2). The organic layer was washed with saturated aqueous NaCl (20 ml), and dried over $MgSO_4$. Concentration *in vacuo* gave the residue, which was purified by silica gel column chromatography with benzene-Et_2O (3:1) to give racemic 2-phenyl-1-(2-thiazolyl)ethanol (rac-**12**) (86 mg, 93%) as a white solid.

b) HPLC Analysis 2-Phenyl-1-(2-thiazolyl)ethanol (**12**) (1.5 mg) was dissolved in isopropanol (0.25 ml), and 1 μl of the solution was subjected to HPLC analysis using chiral Opti-Pak TA (i. d. 3.9 × 300 mm) (flow rate, 1.0 ml/min; eluate, hexane : isopropanol = 30:1; detection UV 254 nm). The racemic 2-phenyl-1-(2-thiazolyl)ethanol (rac-**12**) showed two peaks at R.T. = 23.5 min (R-form) and 26.7 min (S-form).

c) With (+)-Diisopinocampheylchloroborane ((+)-Ipc$_2$BCl, (11g)).[10] (+)-Ipc$_2$BCl (**11g**, 3.92 g, 12.2 mmol) was transferred to the flask under argon rapidly and dissolved in Et_2O (3 ml). To the solution was added benzyl 2-thiazolyl ketone (**9**) (828 mg, 4.08 mmol) in Et_2O (17 ml) at 0°C. The reaction mixture was stirred at 0°C for 23 h. Aqueous NaOH (10%, 10 ml) and then 30% aqueous H_2O_2 were added to the reaction mixture at 0°C and 10°C, respectively. The mixture was stirred at room temperature for 2 h, and diluted with water (50 ml). The aqueous layer was saturated with anhydrous K_2CO_3, and extracted with Et_2O (200 ml × 2, 100 ml × 1). The combined organic extracts were washed with saturated aqueous NaCl (50 ml) and dried over $MgSO_4$. Concentration *in vacuo* gave the residue, which was purified by silica gel column chromatography with hexane-AcOEt (2:1) to give (R)-**12** (665 mg, 80%, 93% ee (R)) as a white solid. The solid was recrystallized to give pure 2-phenyl-1-(2-thiazolyl)ethanol ((R)-**12**) (100% ee (R)) as colorless crystals, mp 89-89.5°C (Et_2O-hexane), bp 160°C/0.9 mmHg, $[\alpha]^{24.5}_D$ + 54.0° (c 1.00, $CHCl_3$). IR (nujol): 3140, 1505, 737, 704 cm.$^{-1}$ ^{1}H-NMR ($CDCl_3$) δ: 2.75 (br, 1H disappeared with D_2O), 3.10 (dd, 1H, J=13.9, 8.5 Hz), 3.38 (dd, 1H, J=13.9, 4.2 Hz), 5.25 (dd, 1H, J=8.5, 4.3 Hz), 7.23-7.34 (m, 6H), 7.76 (d, 1H, J=3.1 Hz). Anal. Calcd for $C_{11}H_{11}NOS$: C, 64.36; H, 5.40; N, 6.82. Found: C, 64.39; H, 5.49; N, 6.74.

d) (S)-2-Phenyl-1-(2-thiazolyl)ethanol ((S)-12). Prepared from benzyl 2-thiazolyl ketone (**9**) (100 mg, 0.49 mmol), and (-)-Ipc$_2$BCl (**11f**, 536 mg, 1.67 mmol) in THF (1 ml) as described in the preparation of (R)-**12**. A white solid (75 mg, 74%, 93% ee (S)) was obtained. The solid was recrystallized to give pure 2-phenyl-1-(2-thiazolyl)ethanol ((S)-**12**) (100% ee (S)) as colorless crystals, mp 84-85°C (Et_2O-hexane). $[\alpha]^{22}_D$ - 53.8° (c 0.99, $CHCl_3$). Anal. Calcd for $C_{11}H_{11}NOS$: C, 64.36; H, 5.40; N, 6.82. Found: C, 64.51; H, 5.40; N, 6.50.

e) With the Borane Complex of (S)-(-)-2-Amino-3-methyl-1,1-diphenylbutanol (Itsuno's reagent, 11a). To a stirred solution of (S)-(-)-2-amino-3-methyl-1,1-diphenylbutanol (**11a**, 155 mg, 0.61 mmol) in THF (0.25 ml) at 0°C was added dropwise borane-THF (1M in THF, 1.5 ml, 1.5 mmol) and the reaction mixture was stirred at 0°C for 8 h.[9] A solution of benzyl 2-thiazolyl ketone (**9**) (100 mg, 0.49 mmol) in THF (0.5 ml) was added dropwise. The mixture was stirred at 0°C for 0.5 h and then cooled with ice-water. After gradual addition of 2 M HCl (4 ml), the mixture was concentrated *in vacuo*. The white solid (S)-(-)-

2-amino-3-methyl-1,1-diphenylbutanol hydrochloride was collected on a glass filter and washed with Et_2O (50 ml). The filtrate was washed with water (10 ml) and saturated aqueous NaCl (20 ml) and dried over $MgSO_4$. Concentration *in vacuo* gave the residue, which was purified by silica gel column chromatography with benzene-Et_2O (2:1) to give a white solid (141 mg). After the solid was dissolved in MeOH (4 ml), 10% aqueous NaOH (5 ml) was dropwise added at 0°C. The mixture was stirred at room temperature for 0.5 h and at 50°C for 22 h. Et_2O was added to the reaction mixture and the separated aqueous layer was extracted with Et_2O (30 ml × 2). The combined Et_2O extracts were washed with saturated aqueous NaCl and dried over $MgSO_4$. Concentration *in vacuo* gave the residue, which was purified by silica gel column chromatography to give 2-phenyl-1-(2-thiazolyl)-ethanol (**12**) (80 mg, 79%, 30% ee(R)) as a white powder.

f) With (S)-5,5-Diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (Corey's reagent, (S)-11b). To a solution of (S)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine ((S)-**11b**, 6.9 mg, 0.025 mmol) in THF (0.2 ml) was added dropwise borane-THF (1 M in THF, 0.05 ml, 0.05 mmol) at room temperature under argon atmosphere.[14] Benzyl 2-thiazolyl ketone (**9**) (101 mg, 0.50 mmol) in THF (0.5 ml) and then borane-THF (1 M in THF, 0.55 ml, 0.55 mmol) was added dropwise to the reaction mixture. The mixture was stirred at room temperature for 15 min and then cooled with ice-water. After addition of 2 M HCl (1 ml), the mixture was concentrated *in vacuo*. The residue was extracted with Et_2O (20 ml × 2). The organic layer was dried over $MgSO_4$. Concentration *in vacuo* gave the residue, which was purified by silica gel column chromatography with benzene-Et_2O (1:1) to give a white solid (62 mg). The white solid was dissolved in MeOH (1 ml) and 10% aqueous NaOH (5 ml) was added dropwise at room temperature. After being stirred at 50°C for 16.5 h,. the reaction mixture was diluted with water (10 ml) and extracted with Et_2O (30 ml × 2). The organic extracts were washed with saturated aqueous NaCl and dried over Na_2SO_4. Concentration *in vacuo* gave the residue, which was purified by silica gel column chromatography with benzene-Et_2O (1:1) to give 2-phenyl-1-(2-thiazolyl)ethanol (**12**) (57 mg, 56%, 10% ee (R)) as a white powder.

g) With (S)-Alpine-Hydride (11d) or NB-Enantride (11e). Benzyl 2-thiazolyl ketone (**9**) was reduced according to the method reported by H.C. Brown and co-workers[15] or M. M. Midland and co-workers.[16] The reduction with NB-enantride (**11e**) was carried out as follows. To a solution of benzyl 2-thiazolyl ketone (**9**) (99 mg, 0.50 mmol) in THF (6 ml) was added dropwise NB-Enantride (**11e**, 0.5 M in THF, 0.58 ml, 0.58 mmol) at -78°C under argon atmosphere. The reaction mixture was stirred at -78°C for 3 h, and then EtOH (0.15 ml) was added. After removal of the cooling bath, the mixture was gradually warmed to 0°C. The mixture was basified with 10% aqueous NaOH (1 ml) and then 30% aqueous H_2O_2

(0.15 ml) was added. The reaction mixture was stirred at 50°C for 2 h and diluted with water (5 ml). The aqueous layer was saturated with anhydrous K_2CO_3, and the THF layer was separated. The aqueous layer was extracted with Et_2O (30 ml × 2). The combined organic extracts were dried over $MgSO_4$. Concentration *in vacuo* gave the residue, which was purified by silica gel column chromatography with benzene-Et_2O (3:1) to give 2-phenyl-1-(2-thiazolyl)ethanol (**12**) (91 mg, 91%, 44% ee (S)) as a white powder.

(S)-2-Phenyl-1-(2-thiazolyl)ethyl Azide (13). To a solution of (R)-2-phenyl-1-(2-thiazolyl)ethanol ((R)-**12**) (93% ee (R), 651 mg, 3.18 mmol) in THF (30 ml) was successively added at 0°C triphenylphosphine (916 mg, 3.49 mmol), diethyl azodicarboxylate (0.55 ml, 3.52 mmol), and DPPA (0.79 ml, 3.52 mmol).[11,12] After removal of the cooling bath, the mixture was gradually warmed to room temperature, and stirred at room temperature for 48 h. The solvent was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography with benzene-hexane-Et_2O (8:5:1) to give a pale orange oil (830 mg, 93% ee (S)) which was a mixture of 2-phenyl-1-(2-thiazolyl)ethyl azide (**13**) and DPPA. The mixture was used for the next step without further purification. For **13**: IR (film): 3030, 2106, 1184, 966, 733, 700 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 3.17 (dd, 1H, J=14.1, 9.0 Hz), 3.42 (dd, 1H, J=14.1, 5.1 Hz), 5.01 (dd, 1H, J=9.0, 5.1 Hz), 7.21-7.36 (m, 6H), 7.81 (d, 1H, J=3.3 Hz).

Boc-(S)-Dolaphenine (2a). To a solution of triphenylphosphine (1.03 g, 3.94 mmol) in THF (6 ml) was added a mixture (747 mg) of the crude **13** in THF (6 ml) with stirring at 50°C, and the reaction mixture was stirred at 50°C for 2 h. Aqueous ammonia (28%, 9 ml) was added and the reaction mixture was stirred at 50°C for 3 h and diluted with water (50 ml). The mixture was extracted with Et_2O (150 ml × 2). The extracts were washed with 1 N HCl (70 ml). The aqueous layer was cooled with ice-water and adjusted to strongly alkaline with 10% aqueous NaOH. The aqueous layer was extracted with CH_2Cl_2 (200 ml). The extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in dioxane (8 ml). Boc_2O (1.15 g, 5.26 mmol) in dioxane (6 ml) was added at 0°C. The mixture was stirred at room temperature for 14 h and diluted with water (20 ml). The mixture was extracted with Et_2O (60 ml × 2). The extracts were washed with saturated aqueous NaCl (50 ml) and dried over Na_2SO_4. Concentration *in vacuo* gave an orange oil, which was purified by silica gel column chromatography with benzene-Et_2O (6:1) to give Boc-(S)-dolaphenine (**2a**) (579 mg, 67% from **13**, 94% ee (S)) as a white solid. The solid was recrystallized to give pure Boc-(S)-dolaphenine (**2a**) (100% ee (S)) as colorless crystals, mp 91-92°C (acetone-hexane), $[\alpha]^{24.5}_D$ -25.5° (c 0.60, $CHCl_3$). IR (nujol): 3331, 1686, 1522, 1250, 1159, 719 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.40 (s, 9H), 1.46-2.17 (br, 1H, disappeared with D_2O), 3.33 (dd, 2H, J=13.7, 6.0 Hz), 5.31 (br, 1H), 7.08-7.27 (m, 6H), 7.76 (d, 1H, J=3.3 Hz). Anal. Calcd

for $C_{16}H_{20}N_2O_2S$: C, 63.12; H, 6.62; N, 9.20. Found: C, 62.83; H, 6.68; N, 8.92.

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