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A New Asymmetric Synthesis of (S)-Dolaphenine and Its Heteroaromatic Congeners Utilizing (+)-2-Hydroxy-3-pinanone and (-)-3-Hydroxy-2-caranone as Chiral Auxiliaries†

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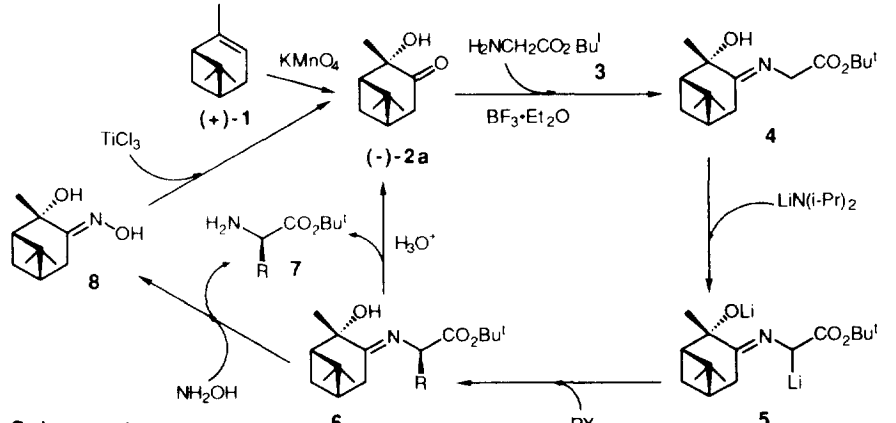
Abstract: (+)-2-Hydroxy-3-pinanone ((+)-HyPN, (+)-**2a**) and (-)-3-hydroxy-2-caranone ((-)-**2b**) were respectively converted to the corresponding Schiff bases **18a** and **18b** with 1-(2-thiazolyl)methylamine (**17**). Alkylation followed by removal of the chiral auxiliaries (+)-**2a** and (-)-**2b** afforded (S)-dolaphenine (**10**) as an optically pure form. The method was applied to the asymmetric synthesis of the dolaphenine analogs **27a-d**.

In 1976, (-)-(1S,2S,5S)-2-hydroxy-3-pinanone ((-)-HyPN, (-)-**2a**) proved to be an efficient chiral auxiliary for the diastereoselective alkylation of the Schiff base derived from glycine tert-butyl ester (**3**).[1] This work together with easy availability of (-)- and (+)-HyPN from (+)- and (-)-α-pinenes (**1**), respectively, has provided an efficient, convenient method for the asymmetric synthesis of α-amino acids, as shown in Scheme 1. One of the prominent feature of the method is the proliferation of the asymmetry by the recycle use of the chiral auxiliary HyPN through recovery from the alkylated Schiff base **6** directly or via the oxime **8**. Later investigations have revealed that this method can be applied to efficient syntheses for not only chiral amino acids,[1,2] but also chiral amines[3] and chiral aminophosphonic acids.[4] These efforts have culminated in commercial availability[5] of both (-)-HyPN and its antipodal (+)-HyPN though they are easily prepared from (+)- and (-)-α-pinenes, respectively.[6]



Scheme 1

† Dedicated to Emeritus Professor Shun-ichi Yamada on the occasion of his 80th birthday (San-ju).

We have already accomplished an efficient synthesis of dolastatin 10 (**9**), a promising antitumor agent of marine origin (Figure 1).[7,8] In this synthesis, we have developed[9] the method for the construction of (S)-dolaphenine (**10**), the C-terminal unit of **9**, in four ways. We now wish to report an application of the asymmetric alkylation method using (+)-HyPN to an efficient synthesis of **10**. Asymmetric synthesis of heteroaromatic analogs of **10** will also be presented. Furthermore, the results of investigation on the use of (-)-3-hydroxy-2-caranone ((-)-**2b**) in place of HyPN as a chiral auxiliary in the asymmetric alkylation will be described.

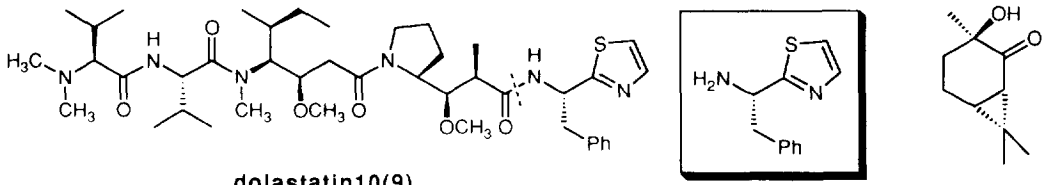
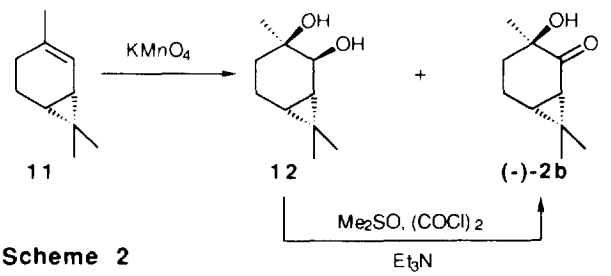


Figure 1

(1) Preparation of Chiral Auxiliaries

(+)-HyPN ((+)-**2a**) was prepared from (-)-α-pinene ((-)-**1**) by its treatment with potassium permanganate according to the literature.[6] Analogous oxidation of 2-carene (**11**) with potassium permanganate afforded (-)-3-hydroxy-2-caranone ((-)-**2b**) in low yield. The major product proved to be (2S,3R)-2,3-dihydroxycarane (**12**). However, the diol **12** was easily converted to (-)-**2b** by the Swern oxidation in good yield, as shown in Scheme 2.



Scheme 2

(2) Asymmetric Synthesis of (S)-Dolaphenine

2-Aminomethylthiazole (**17**), a starting material for the formation of the chiral Schiff base with (+)-HyPN, was prepared by the Hantsch method, as shown in Scheme 3. N-Benzyloxycarbonylglycine amide (**13**) was first transformed to the corresponding thioamide **15** by use of the Lawesson's reagent **14** in almost quantitative yield. The thioamide **15** underwent the Hantsch thiazole synthesis[9,10] with bromoacetaldehyde to give the benzyloxycarbonyl (Z) derivative **16** in good yield. After acidic deprotection of the Z group, the resulting 2-aminomethylthiazole (**17**) was smoothly condensed with (+)-HyPN ((+)-**2a**) to give the Schiff base **18a**. Analogously, the Schiff base **18b** was prepared from (-)-**2b**, as shown in Scheme 3.

Asymmetric alkylation of the chiral Schiff bases **18a** and **18b** with benzyl halides was investigated as shown in Tables 1 and 2, respectively. The desired benzylated product **19a** was obtained with excellent diastereoisomeric excess (de) (>94% de) from **18a** derived from (+)-HyPN ((+)-**2a**) while **18b** derived from the caranone **2b** afforded **19b** with lower diastereoisomeric excess. The dibenzylated products **20a** and **20b** whose structures were determined by their ^{1}H NMR spectra were also formed in many cases, especially when the reactions were carried out at 0°C. Benzyl bromide and n-butyllithium were more preferable than benzyl chloride and lithium diisopropylamide (LDA), respectively. The lower reaction temperature (-78°C) gave the more efficient diastereoselectivity than the higher one (0°C). So far, the most favorable result was obtained by lithiation of **18a** with n-butyllithium followed by treatment with benzyl bromide at -78°C for 2 h, giving **19a** in 69% yield with 97% de.

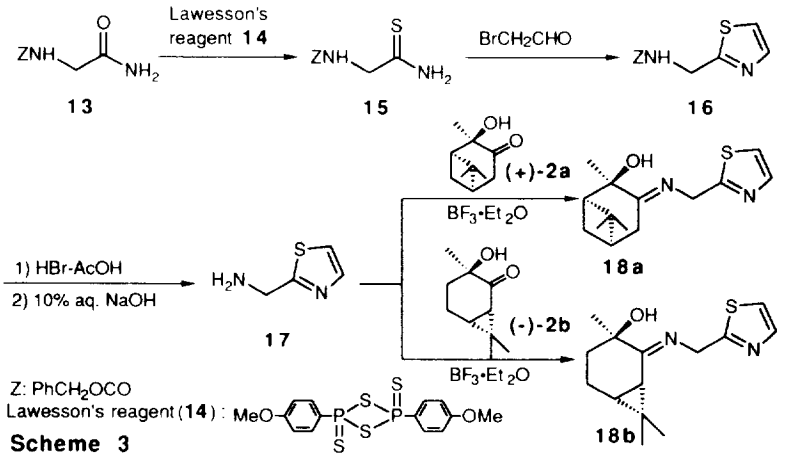
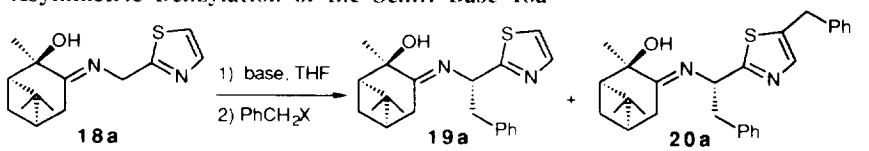


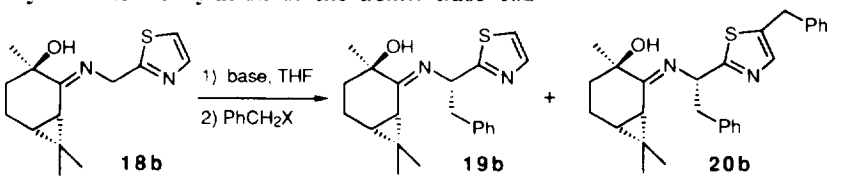
Table 1. Asymmetric Benzylation of the Schiff Base 18a



Run	Base (3 eq)	X	Reaction Temp. (°C)	Reaction Time (h)	Reaction Products 19a Yield (%)	19a de (%)[a]	20a Yield (%)	20a de (%)[a]	Recovery of the Schiff Base (%)
1	n-BuLi	Cl	-78	6	46	97	0	-	33
2	n-BuLi	Cl	0	1	52	97	3	87	0
3	n-BuLi	Br	-78	2	69	97	3	82	0
4	n-BuLi	Br	0	0.5	47	97	27	89	0
5	n-BuLi[b]	Br	0	0.5	47	94	9	84	8
6	LDA	Br	0	0.5	22	94	44	100	0
7	LDA[b]	Br	0	0.5	47	96	9	96	30

a) Determined by ^{1}H NMR spectral analysis. b) 2.2 equiv.

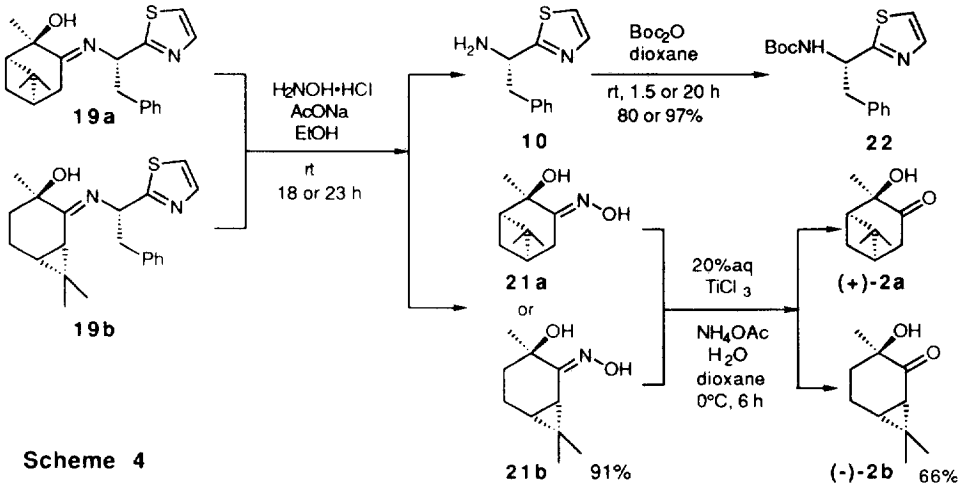
Table 2. Asymmetric Benzylation of the Schiff Base 18b



Run	Base (3 eq)	X	Reaction Temp. (°C)	Reaction Time (h)	Reaction Products 19b Yield (%)	19b de (%)[a]	20b Yield (%)	20b de (%)[a]	Recovery of the Schiff Base (%)
1	n-BuLi	Cl	-78	6	3	82	0	-	90
2	n-BuLi	Cl	0	6	82	4	0	-	11
3	n-BuLi	Br	-78	6	42	76	13	72	29
4	n-BuLi	Br	0	6	45	60	20	-	18

a) Determined by ^{1}H NMR spectral analysis.

Efficient removal of the chiral auxiliaries from the alkylated Schiff bases **19a** (97% de) and **19b** (99.7% de) was respectively accomplished by their treatment with hydroxylamine[1] to give (S)-dolaphenine (**10**). Incidentally, the chiral auxiliaries were recovered as their oxime derivatives **21a** and **21b**, which were converted to (+)-HyPN ((+)-**2a**) and (-)-3-hydroxy-2-caranone ((-)-**2b**), respectively, with titanium trichloride.[1b] (S)-Dolaphenine (**10**) was fully characterized as its optically pure tert-butyloxycarbonyl (Boc) derivative **22**, as shown in Scheme 4. Thus we could complete another efficient synthesis of (S)-dolaphenine (**10**).

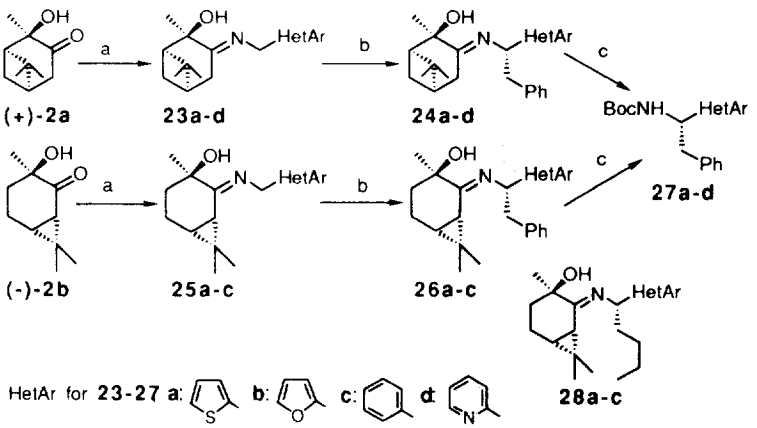


Scheme 4

(3) Asymmetric Synthesis of Analogs of (S)-Dolaphenine

Analogously, the dolaphenine analogs containing the other heteroaromatic (HetAr) and phenyl groups in place of the thiazolyl group were synthesized. The overall synthetic strategy was quite similar to that for (S)-dolaphenine (**10**), as outlined in Scheme 5.

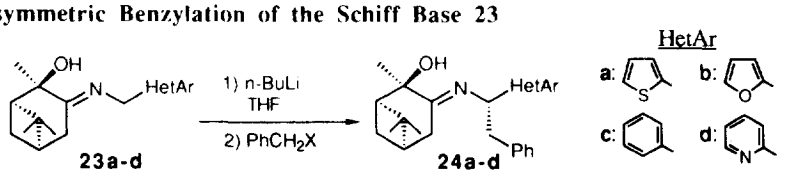
The chiral Schiff bases **23** and **25**, prepared by treatment of arylmethylamines with (+)-HyPN ((+)-**2a**) and (-)-3-hydroxy-2-caranone ((-)-**2b**), respectively, were lithiated with n-butyllithium and alkylated with benzyl halides. As summarized in Tables 3 and 4, benzyl chloride was generally more effective than benzyl bromide in contrast to the benzylation of **18**. Alkylation of the thienyl derivative **23a** sluggishly proceeded to



(a) H_2NCH_2HetAr, BF_3•Et_2O, benzene, reflux (b) i) n-BuLi, THF; ii) Ph CH_2X
(c) i) NH_2OH•HCl, AcONa, EtOH, rt; ii) Boc_2O, dioxane, rt

Scheme 5

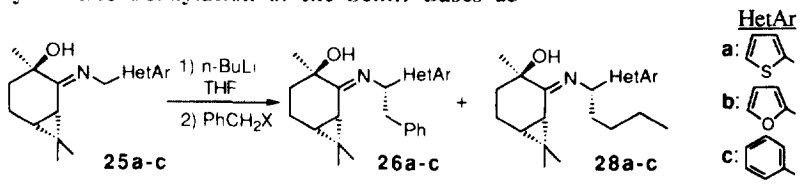
Table 3. Asymmetric Benzylation of the Schiff Base 23



Run	Starting Material	X	Reaction Temp. (°C)	Time (h)	Reaction Product **24** Yield (%)	de (%)[a]	Recovery of the Schiff Base (%)
1	**23a**	Cl	-78	6	5	92	79
2	**23a**	Cl	0	19	14	79	54
3	**23a**	Br	-78	6	2	90	69
4	**23a**	Br	0	20	7	44	72
5	**23b**	Cl	-78	6	66	92	9
6	**23b**	Cl	0	3	67	>98	0
7	**23b**	Br	-78	6	28	>98	19
8	**23c**	Cl	-78	6	30	94	44
9	**23c**	Cl	0	20	22	92	45
10	**23c**	Br	-78	6	-	-	70
11	**23d**	Cl	-78	6	42	>98	0
12	**23d**	Cl	0	2	91	96	0
13	**23d**	Br	-78	2	84	95	0
14	**23d**	Br	0	1	85	92	0

a) Determined by ^{1}H NMR spectral analysis.

Table 4. Asymmetric Benzylation of the Schiff Bases 25



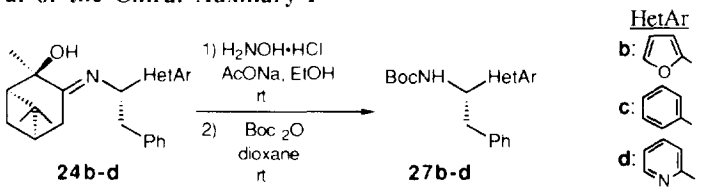
Run	Starting Material	X	Reaction Temp. (°C)	Time (h)	Reaction Product **26** Yield (%)	de (%)[a]	Reaction Product **28** Yield (%)	de (%)[a]	Recovery of the Schiff Base (%)
1	**25a**	Cl	-78	6	28	87	0	-	72
2	**25a**	Cl	0	22	60	70	0	-	25
3	**25a**	Br	-78	6	6	86	18	90	66
4	**25a**	Br	0	21	7	70	31	82	37
5	**25b**	Cl	-78	2	54	84	0	-	25
6	**25b**	Cl	0	0.5	58	80	0	-	0
7	**25b**	Br	-78	2	9	66	30	85	73
8	**25b**	Br	0	0.5	20	74	27	81	37
9	**25c**	Cl	-78	6	75	67	0	-	22
10	**25c**	Cl	0	23	70	29	0	-	22
11	**25c**	Br	-78	6	21	60	43	95	38
12	**25c**	Br	0	1	11	48	89	88	0

a) Determined by ^{1}H NMR spectral analysis.

give the alkylated product **24a**. Most of the HyPN derivatives **23** gave the more favorable results on diastereoselectivity than the caranone derivatives **25**. So far, the alkylation of the pyridyl derivative **23d** most smoothly afforded the benzylated product **24d** with excellent diastereoselectivity. One of the most interesting results in the alkylation was the formation of the butylated products **28** when the Schiff bases **25** derived from the caranone (-)-**2b** were alkylated. This might be due to the formation of butyl halides by lithium-halogen exchange between n-butyllithium and benzyl halides when insufficient lithiation occurred at the methylene group adjacent to the imino nitrogen atom. Use of an excess of n-butyllithium in the lithiation would also cause lithium-halogen exchange. The structures of the butylated products **28a-c** were confirmed by the identification with the products obtained by the butylation of **25a-c** with butyl bromide.

Finally, removal of the chiral auxiliaries from the benzylated Schiff bases **24** and **26** was easily carried out with hydroxylamine as in the case of dolaphenine synthesis. The Boc protection of the resulting amines afforded the Boc derivatives **27a-d**, shown in Tables 5 and 6.

Table 5. Removal of the Chiral Auxiliary-1

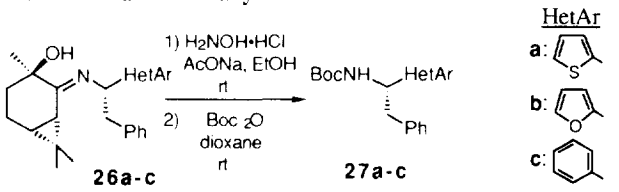


24b-d **27b-d**

Run	Starting Material	De (%) of the Starting Material	Reaction Time (h) Step 1)	Step 2)	Reaction Product **27** Yield (%)	ee (%)	Config.[a]
1	**24b**	92	7	3	67	98[b]	S
2	**24c**	94	19	4	64	>98[c]	S
3	**24d**	95	4	15	60	>98[c]	S

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

Table 6. Removal of the Chiral Auxiliary-2.



26a-c **27a-c**

Run	Starting Material	De (%) of the Starting Material	Reaction Time (h) Step 1)	Step 2)	Reaction Product **27** Yield (%)	ee (%)	Config.[a]
1	**26a**	86	23	24	69	85[b]	S
2	**26b**	80	18	18	63	81[b]	S
3	**26c**	67	24	21	82	69[c]	S

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

In conclusion, we have accomplished a new asymmetric synthesis of (S)-dolaphenine (**10**), the C-terminal residue of antitumor dolastatin 10 (**9**), by the diastereoselective alkylation of the Schiff bases derived from (+)-HyPN ((+)-**2a**) and the caranone (-)-**2b**. The analogs **27a-d** of (S)-dolaphenine have been also synthesized by the analogous procedure.

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 SHIMADZU FT IR-8100 spectrometer. ^{1}H NMR spectra were recorded on a JEOL 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 high-pressure liquid chromatograph and 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. Tetrahydrofuran (THF) was dried by distillation from benzophenone ketyl. Other solvents were distilled and stored over molecular sieves (4A).

(+)-(1R,2R,5R)-2-Hydroxy-3-pinanone ((+)-2a). Prepared from (1S,5S)-(-)-α-pinene according to the literature.[6] The crude ketol was purified by silica gel column chromatography with hexane-ethyl acetate (5:1) to give (1R,2R,5R)-(+)-2-hydroxy-3-pinanone as a white solid. The solid was recrystallized four times to give pure (1R,2R,5R)-(+)-2-hydroxy-3-pinanone ((+)-**2a**), mp 29-30°C (from hexane), $[\alpha]_D^{24}$ +38.3°(c 2.64, $CHCl_3$) [lit.[1b] for (-)-**2a**, mp 31-32°C (from pentane), $[\alpha]_D^{25}$ -38.9° (c 2.64, $CHCl_3$)].

Oxidation of (+)-2-Carene. To a solution of (+)-2-carene (**11**, 4.00 g, 29.4 mmol) in t-butyl alcohol (80 ml) and water (40 ml) was added dropwise a solution of $KMnO_4$ (5.76 g, 36.5 mmol) and NaOH (1.29 g, 32.2 mmol) in H_2O (120 ml) below 10°C, and the reaction mixture was stirred at 0°C for 15 min. The insoluble materials were removed by filtration and washed with AcOEt (200 ml × 2). The filtrate was concentrated *in vacuo* and the residue was saturated with NaCl and extracted with AcOEt (300 ml × 2) and dried over Na_2SO_4. Concentration *in vacuo* gave the residue, which was purified by silica gel column chromatography with hexane-Et_2O (1:10 → 0:1) to give (-)-carane-2,3-diol (**12**) (3.95 g, 79%) as a white solid and (-)-3-hydroxy-2-caranone ((-)-**2b**, 180 mg, 3.6%) as a colorless oil.

(-)-Carane-2,3-diol (12), mp 52-54°C, bp 170-175°C/6 mmHg, $[\alpha]_D^{24.5}$ -7.66° (c 1.00, $CHCl_3$). IR ν_{max} (nujol): 3336, 2922, 1373, 1343, 1275, 1132, 1061, 1049, 922 cm^{-1}. ^{1}H NMR($CDCl_3$) δ: 0.57(dd, 1H, J=2.6, 9.2 Hz), 0.77 (t, 1H, J=8.4 Hz), 0.96 (s, 3H), 1.06 and 1.00-1.21 (s and m, 4H), 1.23(s, 3H), 1.54-1.69 (m, 2H), 1.84-2.00 (m, 1H), 2.17 (brs, 1H, disappeared with D_2O), 2.54 (brs, 1H, disappeared with D_2O), 3.18 (s, 1H). ^{13}C NMR ($CDCl_3/CHCl_3$) δ: 14.83, 14.90, 16.57, 19.91, 25.64, 26.54, 28.97, 34.11, 70.08, 71.02.

(-)-3-Hydroxy-2-caranone ((-)-2b), bp 140-145°C/6 mmHg, $[\alpha]_D^{24.5}$ -138.2° (c 1.01, $CHCl_3$). IR ν_{max} (film): 3418, 2987, 1696, 1454, 1378, 1333, 1125, 1046, 916 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 1.15 and 1.16 (s × 2, 6H), 1.27 (s, 3H), 1.45 (td, 1H, J=3.3, 7.3 Hz), 1.54 (d, 1H, J=7.6 Hz), 1.61-1.83 (m, 2H), 1.89-2.07 (m, 1H), 2.14-2.24 (m, 1H), 2.70-2.90 (br, 1H). ^{13}C NMR ($CDCl_3/CHCl_3$) δ: 16.61, 17.76, 24.01, 26.67, 28.41, 30.10, 33.39, 35.49, 75.03, 211.07. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59; N, 0.00. Found: C, 71.34; H, 9.64; N, 0.00.

Oxidation of (-)-Carane-2,3-diol (12). To a solution of oxalyl chloride (0.6 ml, 6.88 mmol) in CH_2Cl_2 (10 ml) was added DMSO (1.5 ml, 21.2 mmol) at -78°C, and the mixture was stirred at -78°C for 0.5 h. A solution of (-)-carane-2,3-diol (**12**, 170 mg, 0.998 mmol) in CH_2Cl_2 (3 ml) was added at -78°C, and the mixture was stirred at -78°C for 1 h, and then TEA (4.2 ml, 30.0 mmol) was added. After the mixture was stirred at 0°C for 3 hr, water (30 ml) was added, and the mixture was extracted with CH_2Cl_2 (30 ml × 2). The 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 hexane-Et_2O (1:7) to give (-)-3-hydroxy-2-caranone ((-)-**2b**) as a colorless oil (137 mg, 81.5 %).

Preparation of 2-Aminomethylthiazole (17)

N-Benzyloxycarbonylglycine thioamide (15). A mixture of N-benzyloxycarbonylglycine amide (**13**, 408 mg, 1.96 mmol) and the Lawesson's reagent (**14**, 436 mg, 1.08 mmol) in dioxane (3 ml) was heated to 60°C for 30 min and then stirred at ambient temperature for 3 h. After removal of the volatiles, a mixture of saturated aqueous $NaHCO_3$ and water (1:1, 10 ml) was added. The resulting white solid was collected and washed with water to give **15** (444 mg, quantitative), mp. 122-125°C. IR ν_{max} (nujol): 3387, 3295, 3150, 2924, 1684, 1626, 1539, 1287, 1248 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 4.17 (d, 2H, J=5.9 Hz), 5.13 (s, 2H), 6.52

(br, 1H), 7.33-7.37 (m, 5H), 8.41 and 8.60 (2 × br, 2H). High mass calcd for $C_{10}H_{12}N_2OS$: 224.06194. Obsd: 224.06163.

2-(N-(Benzyloxycarbonyl)aminomethyl)thiazole (16). A solution of bromoacetaldehyde in DMF (30 ml) was prepared as followed: diethyl bromoacetal (2.310 g, 11.72 mmol) was hydrolyzed with concentrated hydrochloric acid (2.3 ml) between 55 and 60°C for 30 min. The mixture was cooled to about 10°C, and dried with molecular sieves 3A (11.5 g) in DMF (30 ml). The solution, after decantation, was used without further purification. The bromoacetaldehyde solution thus prepared was added dropwise to **15** and the mixture was stirred at 60°C for 6 h. The mixture was diluted with ethyl acetate and benzene (5:1, 100 ml), washed with saturated aqueous $NaHCO_3$ (50 ml), H_2O (50 ml) and saturated aqueous NaCl (50 ml), and dried over $MgSO_4$. Concentration *in vacuo* followed by silica gel column chromatography of the evaporated residue with benzene-Et_2O (1:1) afforded **16** as a brown oil (1.025 g, 71%). Distillation at 180°C/ 7 mmHg furnished **16** as a colorless oil. IR ν_{max} (film): 3320, 1717, 1540, 1256, 1142, 735 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 4.68 (d, 2H, J=6.3 Hz), 5.14 (s, 2H), 5.82 (br, 1H), 7.27 (d, 1H, J=3.6 Hz), 7.34 (s, 5H), 7.70 (d, 1H, J=3.3 Hz). High mass calcd for $C_{12}H_{12}N_2O_2S$: 248.06194. Obsd: 248.06159.

2-Aminomethylthiazole (17). The thiazole **16** (4.234 g, 17.05 mmol) was treated with 25% HBr in AcOH (57 ml) at room temperature for 1 h. Dry diethyl ether was added to the mixture, and the mixture was allowed to stand at room temperature for at least 10 minutes to give the brown precipitates. The precipitates were dissolved in H_2O (50 ml), basified with 10% aqueous NaOH, and extracted with methylene chloride (150 ml x 3). The organic extracts were washed with saturated aqueous NaCl (150 ml), and dried over Na_2SO_4. Concentration *in vacuo* gave a yellow oil (1.770 g, 91%), which was purified by distillation at 85°C/ 7 mmHg to give **17** as a colorless oil (1.464 g). IR ν_{max} (film): 3368, 1607, 1505, 1190, 1138, 1061, 876, 725 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.78 (s, 2H, disappeared with D_2O), 4.21 (s, 2H), 7.27 (d, 1H, J=3.6 Hz), 7.72 (d, 1H, J=3.3 Hz). High mass calcd for $C_4H_6N_2S$: 114.02517. Obsd: 114.02524.

Preparation of the Schiff Bases 18, 23, and 25.

Schiff Base 18a of 2-Aminomethylthiazole. A mixture of 2-aminomethylthiazole (**17**, 300 mg, 2.63 mmol) and (+)-HyPN ((+)-**2a**, 502 mg, 2.98 mmol) in benzene (6 ml) containing boron trifluoride etherate (0.06 ml) was refluxed for 2 hr using a Cope apparatus (molecular sieves type 4A) under argon. The solvent was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography with benzene-Et_2O (1:1→0:1) to give **18a** (540 mg, 78%) as a white solid, mp 80-83°C, $[\alpha]_D^{22.5}$ -27.3°(c 1.00, MeOH). IR ν_{max} (nujol): 3249, 2855, 1655, 1464, 1366, 1140, 1084, 764 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.87 (s, 3H), 1.35 (s, 3H), 1.57 (s, 3H), 1.59 (d, 1H, J=13.2 Hz), 2.07-2.14 (m, 2H), 2.35-2.41 (m, 2H, disappeared with D_2O), 2.61 (s, 2H), 4.78 (AB q, 2H, J=19 Hz), 7.29 (d, 1H, J=3.3 Hz), 7.77 (d, 1H, J=3.0 Hz). High mass calcd for $C_{14}H_{20}N_2OS$: 264.12963. Obsd: 264.12867.

Schiff Base 23a of 2-Methylaminothiophene. Prepared analogously from 2-aminomethylthiophene at reflux for 1.5 h. A crude yellow oil was purified by silica gel column chromatography with hexane-Et_2O (1:1) to give **23a** (92%) as a pale yellow oil, $[\alpha]_D^{24.5}$ -16.7° (c 1.11, $CHCl_3$). IR ν_{max} (film): 3424, 2919, 1651, 1370, 1161, 1084 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.87 (s, 3H), 1.53 (s, 3H), 1.58 (d, 1H, J=11 Hz), 2.02-2.12 (m, 2H), 2.31-2.40 (m, 1H), 2.51 (br, 1H, disappeared with D_2O), 2.61 (t, 2H, J=18 Hz), 4.70 (t, 2H, J=16 Hz), 5.29-6.99 (m, 2H), 7.19-7.26 (m, 1H). High mass calcd for $C_{15}H_{21}NOS$: 263.13440. Obsd: 263.13600.

Schiff Base 23b of 2-Methylaminofuran. Prepared analogously from 2-methylaminofuran at reflux for 3 h. A column chromatography of the crude product with hexane-ethyl acetate (2:1→1:1) gave **23b** (quantitative) as a white solid, mp 45-47°C, $[\alpha]_D^{26}$ -1.89° (c 1.01, $CHCl_3$). IR ν_{max} (film): 3420, 2923, 1653, 1370, 1148, 1084, 1013, 924, 731 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.87 (s, 3H), 1.34 (s, 3H), 1.50 (s, 3H), 1.58 (d, 1H, J=11 Hz), 2.05-2.13 (m, 1H), 2.15-2.25 (br, 1H, disappeared with D_2O), 2.32-2.39 (m, 1H), 2.64 (t, 2H, J=21 Hz), 4.49 (t, 2H, J=17 Hz), 6.22-6.30 (m, 1H), 6.33-7.26 (m, 1H), 7.35-7.37 (m, 1H). High mass calcd for $C_{15}H_{21}NO_2$: 247.15722. Obsd: 247.15476.

Schiff Base 23c of Benzylamine. Prepared analogously from benzylamine at reflux for 4 h. A crude pale yellow oil was purified by silica gel column chromatography with hexane-Et_2O (1:1) to give **23c** (93%) as a colorless oil, $[\alpha]_D^{25}$ -6.50° (c 1.02, $CHCl_3$). IR ν_{max} (film): 3419, 2919, 1651, 1370, 1084, 754

cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.87 (s, 3H), 1.34 (s, 3H), 1.54 (s, 3H), 1.59 (d, 1H, J=11 Hz), 2.03-2.13 (m, 2H), 2.32-2.41 (m, 1H), 2.61 (t, 3H, J=19 Hz, disappeared with D_2O), 4.53 (t, 2H, J=17 Hz), 7.22-7.39 (m, 5H).

Schiff Base 23d of 2-Aminomethylpyridine. Prepared analogously from 2-aminomethylpyridine at reflux for 1 h. A crude yellow oil was purified by silica gel column chromatography with methylene chloride-hexane-ethanol (13:2:1) to give **23d** (quantitative) as a white solid, mp. 44-47°C, $[\alpha]_D^{26}$ -13.8° (c 1.00, $CHCl_3$). IR ν_{max} (film): 3379, 2980, 1651, 1593, 1476, 1435, 1370, 1161, 1084, 758 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.88 (s, 3H), 1.34 (s, 3H), 1.55 (s, 3H), 1.59 (d, 1H, J=11Hz), 2.04-2.13 (m, 2H), 2.33-2.41 (m, 1H), 2.41-2.61 (br, 1H, disappeared with D_2O), 2.64 (s, 2H), 4.66 (t, 2H, J=19 Hz). 7.15-7.20 (m, 1H), 7.55 (d, 1H, J=7.6 Hz), 7.70 (td, 1H, J=1.7, 7.6Hz), 8.55 (m, 1H). High mass calcd for $C_{16}H_{22}N_2O$: 258.17320. Obsd: 258.17262.

Schiff base 18b of 2-Aminomethylthiazole. A crude brown oil was purified by Florisil (Nakarai mesh 60-100) column chromatography with hexane-AcOEt (1:5) to give the Schiff base **18b** (72 %) as an orange solid, mp 63-65°C, $[\alpha]_D^{24}$ -263.0° (c 0.51, $CHCl_3$). IR ν_{max} (nujol): 3380, 2924, 1646, 1509, 1456, 1331, 1142, 1117, 910, 737 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.92 (s, 3H), 1.23 and 1.15-1.30 (s and m, 5H), 1.45 and 1.35-1.62 (s and m, 5H), 1.79-2.05 (m, 1H), 2.13-2.22 (m, 1H), 2.48 (brs, 1H, disappeared with D_2O), 4.82 (ABq, 2H, J=18.5 Hz), 7.28 (d, 1H, J=3.3 Hz), 7.77 (d, 1H, J=3.3 Hz). MS m/z: 264 (M^+), 263, 246 (M^+-H_2O), 193, 166, 148, 124, 98.

Schiff base 25a of 2-Methylaminothiophene. A crude pale yellow oil was purified by Florisil column chromatography with hexane-AcOEt (5:1) to give the Schiff base **25a** (83 %) as a pale yellow oil, $[\alpha]_D^{24.5}$ -280.0° (c 1.01, $CHCl_3$). IR ν_{max} (film): 3412, 2940, 1644, 1453, 1375, 1316, 1121, 916 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.91 (s, 3H), 1.21 (s, 3H), 1.23-1.34 (m, 2H), 1.40 (s, 3H), 1.41-1.44 (m, 1H), 1.45-1.62 (m, 1H), 1.77-1.87 (m, 1H), 2.05-2.21 (m, 1H), 2.55 (s, 1H, disappeared with D_2O), 4.74 (ABq, 2H, J=16.3 Hz), 6.94-6.99 (m, 2H), 7.19-7.26 (m, 1H). High mass calcd for $C_{15}H_{21}NOS$: 263.1344. Obsd: 263.1295.

Schiff base 25b of 2-Methylaminofuran. A crude orange oil was purified by Florisil column chromatography with hexane-AcOEt (4:1 → 0:1) to give the Schiff base **25b** (90%) as a pale yellow oil, $[\alpha]_D^{25}$ -261.1° (c 0.954, $CHCl_3$). IR ν_{max} (film): 3406, 2938, 1644, 1453, 1375, 1335, 1148, 1121, 918, 729 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.94 (s, 3H), 1.21 and 1.15-1.29 (s and m, 4H), 1.40 and 1.41-1.52 (s and m, 5H), 1.54-1.61 (m, 1H), 1.77-1.86 (m, 1H), 2.10-2.20 (m, 1H), 2.61 (br, 1H, disappeared with D_2O), 4.54 (ABq, 2H, J=16.1 Hz), 6.20-6.21 (m, 1H), 6.220-6.223 (m, 1H), 6.33-7.37 (m, 1H). Ms m/z=248 (M^++1), 229 (M^+-H_2O), 167, 149, 96, 81.

Schiff base 25c of Benzylamine. A crude yellow oil was purified by Florisil column chromatography with hexane-AcOEt (3:1 → 0:1) to give the Schiff base **25c** (83.5%) as a pale yellow oil, $[\alpha]_D^{26}$ -270.1° (c 1.01, $CHCl_3$). IR ν_{max} (film): 3413, 2940, 1646, 1495, 1453, 1375, 1121, 916, 733 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.91 (s, 3H), 1.20 and 1.15-1.38 (s and m, 5H), 1.41 and 1.40-1.49 (s and m, 4H), 1.56-1.64 (m, 1H), 1.78-1.92 (m, 1H), 2.09-2.18 (m, 1H), 2.18-2.80 (br, 1H, disappeared with D_2O), 4.59 (ABq, 2H, J=15.8 Hz), 7.23-7.35 (m, 5H). High mass calcd for $C_{17}H_{23}NO$: 257.1780. Obsd: 257.1888.

Benzylation of the Schiff Bases 18, 23, and 25.

Benzylation of the Schiff Base 18a of 2-Aminomethylthiazole. To a stirred solution of the Schiff base **18a** (203 mg, 0.77 mmol) in THF (2 ml) at -78°C under argon was added dropwise a solution of n-butyllithium (1.60 M in hexane, 1.45 ml, 2.32 mmol). The reaction mixture was stirred at -78°C for 3 h, and then benzyl bromide (0.185 ml, 1.56 mmol) in THF (1 ml) was added. After being stirred at -78°C for 2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 ml). The whole was extracted 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 to give the monobenzylated product **19a** (187 mg, 69%) as a pale yellow oil and dibenzylated product **20a** (10 mg, 3%) as a pale yellow oil.

19a: $[\alpha]_D^{27.5}$ -12.0° (c 1.02, $CHCl_3$). IR ν_{max} (film): 3563, 3376, 1653, 1497, 1455, 1370, 1144, 1082, 1057, 924, 754, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.29 (s, 3H), 1.19 (s, 3H), 1.35 (d, 1H, J=10.6 Hz), 1.45 (s, 3H), 1.82 (dt, 1H, J=3.0, 9.2 Hz), 1.92-1.98 (m, 2H), 2.16-2.23 (m, 1H), 2.43 (dd, 1H, J=3.0, 17.8

Hz), 2.65 (s, 1H, disappeared with D_2O), 3.08 (dd, 1H, J=10.3, 12.9 Hz), 3.52 (dd, 1H, J=3.0, 12.9 Hz), 5.26 (dd, 1H, J=3.0, 10.3 Hz), 7.15-7.24 (m, 5H), 7.28 (d, 1H, J=3.3 Hz), 7.79 (d, 1H, J=3.3 Hz). The diastereomeric excess was determined from the ratio of integration at δ 5.26. High mass calcd for $C_{21}H_{26}N_2OS$: 354.17657. Obsd: 354.17719.

20a: IR ν_{max} (film): 3563, 3374, 1653, 1495, 1455, 1369, 1082, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.26 (s, 3H), 1.18 (s, 3H), 1.33 (d, 1H, J=10.6 Hz), 1.14 (s, 3H), 1.50-1.79 (m, 1H), 1.87-1.94 (m, 2H), 2.10-2.21 (m, 1H), 2.41 (dd, 1H, J=17.6, 2.97 Hz), 2.56 (s, 1H, disappeared with D_2O), 3.04 (dd, 1H, J=13.2, 10.3 Hz), 3.48 (dd, 1H, J=13.2, 2.97 Hz), 4.21 (s, 2H), 5.15 (dd, 1H, J=10.6, 2.97 Hz), 7.15-7.35 (m, 10H), 7.47 (s, 1H). The diastereomeric excess was determined from the ratio of integration at δ 5.15. MS m/z: 444 (M^+).

Benzylation of the Schiff Base 23a of 2-Aminomethylthiophene. The crude product was purified by silica gel column chromatography with hexane-Et_2O (10:1) to give the starting **23a** (54%) and the desired **24a** (14%): **24a** (a yellow oil), IR ν_{max} (film): 3554, 3431, 2921, 1651, 1370, 1082, 749 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.30 (s, 3H), 0.70 (s, 3H), 1.19 (s, 3H), 1.34 (d, J=10.6Hz), 1.40 (s, 3H), 1.80-1.85 (m, 1H), 1.95 (t, 1H, J=5.8Hz), 2.04 (dt, 1H, J=17.8, 3.3Hz), 2.64 (brs, 1H), 3.14 (dd, 1H, J=12.9, 9.9Hz), 3.28 (dd, 1H, J=12.9, 3.6Hz), 5.10 (dd, 1H, J=9.9, 3.6Hz), 6,92-6.99 (m, 2H), 7.13-7.27 (m, 6H). The diastereomeric excess was determined from the ratio of integration at δ 5.10. MS m/z: 335 (M^+-H_2O).

Benzylation of the Schiff Base 23b of 2-Aminomethylfuran. The crude product was purified by silica gel column chromatography with hexane-Et_2O (2:1) to give **24b** as a pale yellow oil (69%): **24b**, $[\alpha]_D^{26}$ -113.3° (c 1.02, $CHCl_3$). IR ν_{max} (film): 3435, 1719, 1651, 1454, 1370, 1161, 1084, 926, 745, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.30 (s, 3H), 1.20 (s, 3H), 1.37 (s, 3H), 1.42 (d, 1H, J=10.6Hz), 1.82-1.87 (m, 1H), 1.94 (t, 1H, J=5.9Hz), 2.10 (dt, 1H, J=18.0, 2.7Hz), 2.20-2.24 (m, 1H), 2.25 (dd, 1H, J=3.2, 17.9Hz), 2.52 (s, 1H, disappeared with D_2O), 3.13 (dd, 1H, J=10.2, 13.1Hz), 3.35 (dd, 1H, J=3.5, 13.0Hz), 4.90 (dd, 1H, J=3.3, 10.1Hz), 6.16-6.17 (m, 1H), 6.33 (dd, 1H, J=1.8, 3.1Hz), 7.13-7.26 (m, 5H), 7.37-7.38 (m, 1H). The diastereomeric excess was determined from the ratio of integration at δ 4.90. MS m/z: 319 (M^+-H_2O).

Benzylation of the Schiff Base 23c of Benzylamine. The crude product was purified by silica gel column chromatography with hexane-Et_2O (10:1 to 1:1) to give the starting **23c** (44%) and the desired **24c** as a pale yellow oil (30%): **24c**, $[\alpha]_D^{25}$ -59.3° (c 1.01, $CHCl_3$). IR ν_{max} (film): 3448, 2919, 1651, 1495, 1455, 1370, 1084, 758, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.35 (s, 3H), 1.19 (s, 3H), 1.31 (d, 1H, J=10.2Hz), 1.41 (s, 3H), 1.78-1.84 (m, 1H), 1.94 (t, 1H, J=5.9Hz), 2.05-2.27 (m, 2H), 2.36 (dd, 1H, J=3.0, 17.6Hz), 2.52 (s, 1H, disappeared with D_2O), 3.05-3.20 (m, 2H), 4.80 (dd, 1H, J=4.0, 9.3Hz), 7.11-7.43 (m, 10H). The diastereomeric excess was determined from the ratio of integration at δ 4.80.

Benzylation of the Schiff Base 23d of 2-Aminomethylpyridine. The crude product was purified by silica gel column chromatography with methylene chloride-hexane-ethanol (13:2:1) to give **24d** as a pale yellow oil (91%): **24d**, $[\alpha]_D^{24}$ -67.09° (c 1.01, $CHCl_3$). IR ν_{max} (film): 3380, 2975, 1651, 1591, 1472, 1435, 1082, 1051, 773, 746, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.31 (s, 3H), 1.19 (s, 3H), 1.31 (d, 1H, J=10.4Hz), 1.42 (s, 3H), 1.80-1.84 (m, 1H), 1.94 (t, 1H, J=5.9Hz), 2.06 (dt, 1H, J=12.5, 2.8Hz), 2.15-2.22 (m, 1H), 2.41 (dd, 1H, J=18.0, 3.1Hz), 2.59 (s, 1H), 3.07 (dd, 1H, J=13.0, 10.3Hz), 3.41 (dd, 1H, J=13.0, 3.3Hz), 5.01 (dd, 1H, J=10.3, 3.3Hz), 7.14-7.21 (m, 6H), 7.44 (d, 1H, J=7.9Hz), 7.67 (td, 1H, J=7.7, 1.8Hz), 8.58 (dq, 0.976H, J=4.9, 0.9Hz), 8.50-8.53 (m, 0.024H). The diastereomeric excess was determined from the ratio of integration at δ 5.01. High mass calcd for $C_{23}H_{28}N_2O$: 348.22010. Obsd: 348.21807.

Benzylation of the Schiff Base 18b of 2-Aminomethylthiazole. A yellow oil was purified by silica gel column chromatography with hexane-AcOEt (1:1 → 0:1) to give the (S)-monobenzylated product **(S)-19b**, (R)-monobenzylated product **(R)-19b**, dibenzylated product **20b**, and the starting material.

(S)-19b, a pale yellow oil: $[\alpha]_D^{24}$ -167.8°(c 0.500, $CHCl_3$). IR ν_{max} (film): 3377, 2930, 1640, 1497, 1455, 1125, 918, 754, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.30 (s, 3H), 1.06 (s, 3H), 1.36 and 1.05-1.43 (s and m, 5H), 1.52-1.60 (m, 2H), 1.68-1.78 (m, 1H), 1.96-2.07 (m, 1H), 3.05 (brs, 1H), 3.25 (dd, 1H, J=8.9, 12.9

Hz), 3.39 (dd, 1H, J=4.0, 12.9 Hz), 5.19 (dd, 1H, J=8.9, 4.0 Hz), 7.13-7.26 (m, 6H), 7.75 (d, 1H, J=3.3 Hz), Ms m/z: 353 (M^+-1), 336 (M^+-H_2O), 189, 111, 97, 91, 85.

(R)-19b, a pale yellow solid: mp 85-89°C, $[\alpha]_D^{24}$ -226.2° (C 0.502, $CHCl_3$). IR ν_{max} (nujol): 3359, 2920, 1644, 1470, 1378, 1364, 1142, 1092, 727 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.23(d, 1H, J=8.6 Hz), 0.59 (s, 3H), 0.89 (td, 1H, J=3.0, 8.3 Hz), 0.99 (s, 3H), 1.10-1.25 (m, 1H), 1.43 and 1.25-1.62 (s and m, 4H), 1.67-1.77 (m, 1H), 1.91-2.05 (m, 1H), 2.21 (s, 1H), 3.03 (dd, 1H, J=9.6, 12.9 Hz), 3.49 (dd, 1H, J=3.3, 12.9 Hz), 5.18 (dd, 1H, J=3.3, 3.6 Hz), 7.13-7.33 (m, 6H), 7.79 (d, 1H, J=3.3 Hz). MS m/z: 354 (M^+), 353, 335, 263, 227, 188, 111, 97, 91, 85.

20b, a pale yellow oil: $[\alpha]_D^{24}$ -198.7° (c 0.110, $CHCl_3$) for 72.2% de. IR ν_{max} (film): 3376, 2928, 1640, 1495, 1455, 1372, 1125, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.26 (s, 3H), 1.03 (s, 3H), 1.32 and 1.06-1.37 (s and m, 5H), 1.39-1.80 (m, 3H), 1.82-2.21 (m, 2H), 3.21 (dd, 1H, J=8.9, 12.9 Hz), 3.35 (dd, 1H, J=8.9, 3.6 Hz), 4.11 (s, 2H), 5.08 (dd, 1H, J=8.9, 3.6 Hz), 7.13-7.35 (m, 10H), 7.42 (s, 1H). The diastereomeric excess was determined from the ratio of integration at δ 5.08. MS m/z: 444 (M^+), 443, 426 (M^+-H_2O), 367, 353, 335, 293, 279, 188, 91.

Benzylation of the Schiff Base 25a of 2-Methylaminothiophene. An orange oil was purified by silica gel column chromatography with hexane-AcOEt (4:1 → 0:1) to give the diastereoisomeric mixture of benzylated products **26a** and butylated products **28a**, and the starting material.

26a, a pale yellow oil: $[\alpha]_D^{24.5}$ -246.5° (c 1.00, $CHCl_3$) for 87% de. IR ν_{max} (film): 3433, 2863, 1640, 1454, 1375, 1123, 698 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.41 (s, 3H), 0.90-1.07 (m, 1H), 1.09 (s, 3H), 1.12-1.33 (m, 2H), 1.37 (s, 3H), 1.49-1.58 (m, 1H), 1.66-1.77 (m, 1H), 1.93-2.06 (m, 1H), 2.96 (s, 1H, disappeared with D_2O), 3.12-3.27 (m, 2H), 4.95 (dd, 1H, J=8.3, 5.3 Hz), 6.78 (d, 1H, J=3.6 Hz), 6.89-6.92 (m, 1H), 7.13-7.80 (m, 6H). The diastereomeric excess was determined from the ratio of integration at δ 4.95. MS m/z: 335 (M^+-H_2O), 244, 187, 97, 91.

28a, a pale yellow oil: $[\alpha]_D^{25}$ -299.4° (c 0.505, $CHCl_3$) for 82% de. IR ν_{max} (film): 3432, 2932, 1640, 1455, 1375, 1125, 916, 696 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.90 (t, 3H, J=7.1 Hz), 0.99 (s, 3H), 1.20 and 1.19-1.36 and 1.38 (s and m and s, 13H), 1.60 and 1.43-1.67 (brs and m, 3H), 1.71-1.80 (m, 1H), 1.83-1.91 (m, 1H), 2.01-2.32 (m, 1H), 4.77 (t, 1H, J=7.3 Hz), 6.85 (d, 1H, J=3.6 Hz), 6.91-6.94 (m, 1H), 7.16-7.19 (m, 1H). The diastereomeric excess was determined from the ratio of integration at δ 4.77. High mass calcd for $C_{19}H_{29}NOS$: 319.1970. Obsd: 319.1966.

Benzylation of the Schiff Base 25b of 2-Methylaminofuran. An orange oil was purified by silica gel column chromatography with hexane-Et_2O (1:1) to give a mixture of the diastereoisomers of benzylated products **26b** and butylated products **28b**, and the starting material.

26b, a yellow oil: $[\alpha]_D^{24.5}$ -213.1° (c 0.988, $CHCl_3$) for 81% de. IR ν_{max} (film): 3430, 2930, 1640, 1455, 1375, 1125, 1011, 916, 735, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.33 (s, 3H), 0.53-1.06 (m, 1H), 1.11 (s, 3H), 1.30 and 1.13-1.43 (s and m, 4H), 1.46-1.80 (m, 3H), 1.88-2.54 (m, 1H), 2.99 (brs, 1H), 3.19 (dd, 1H, J=12.9, 8.7 Hz), 3.33 (dd, 1H, J=12.9, 4.6 Hz), 4.79 (dd, 1H, J=4.6, 8.6 Hz), 6.08-6.11 (m, 1H), 6.28-6.32 (m, 1H), 7.12-7.26 and 7.36-7.37 (m, 6H). The diastereomeric excess was determined from the ratio of integration at δ 4.79. High mass calcd for $C_{22}H_{27}NO_2$: 337.2042. Obsd: 337.2027.

28b, a yellow oil: $[\alpha]_D^{25}$ -318.2° (c 0.50, $CHCl_3$) for 85% de. IR ν_{max} (film): 3425, 2934, 1640, 1505, 1455, 1377, 1148, 1125, 1069, 916, 756, 733 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.91 (t, 3H, J=6.9 Hz), 0.98 (s, 3H), 1.19 and 1.36 and 1.05-1.53 (s and s and m, 13H), 1.58-1.67 (m, 1H), 1.72-1.89 (m, 2H), 1.93-2.15 (m, 2H), 2.99 (br, 1H), 4.60 (t, 1H, J=5.9 Hz), 6.08 (d, 1H, J=3.0 Hz), 6.28 (dd, 1H, J=3.0, 2.0 Hz), 7.32 (d, 1H, J=1.7 Hz). The diastereomeric excess was determined from the ratio of integration at δ 4.60. Ms m/z: 303 (M^+), 286, 247, 193, 166, 152, 151, 137, 95, 81.

Benzylation of the Schiff Base 25c of Benzylamine. A colorless oil was purified by silica gel column chromatography with hexane-AcOEt (4:1) to give a mixture of the diastereoisomers of benzylated products **26c** as a colorless oil and butylated products **28c**, and the starting material.

26c, a colorless oil: $[\alpha]_D^{26}$ -209.4° (c 0.998, $CHCl_3$) for 67% de. IR ν_{max} (film): 3438, 2940, 1642, 1493, 1453, 1375, 1223, 758, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.42 and 0.45 (2 × s, 3H), 1.01 and 1.11 (2 × s,

3H), 1.32 and 1.36 (2 × s, 3H), 0.98-1.39 (m, 1H), 1.52-1.72 (m, 1H), 1.94-2.05 (m, 1H), 3.04-3.20 (m, 3H, 1H disappeared with D_2O). 4.61 and 4.77 (2 × dd, 1H, J=4.8, 8.3 Hz), 7.09-7.39 (m, 10H). The diastereomeric excess was determined from the ratio of integration at δ 4.61 and 4.77. MS m/z: 256, 238, 166, 149, 91.

28c, a colorless oil: $[\alpha]_D^{23}$ -217.8° (c 0.760, $CHCl_3$) for 85% de. IR ν_{max} (film): 3433, 2956, 1636, 1453, 1375, 1123, 916, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.88 (t, 3H, J=7.0 Hz), 1.00 (s, 3H), 1.21 and 1.39 and 1.07-1.39 (s and s and m, 14H), 1.61-1.70 (m, 2H), 1.78-1.87 (m, 1H), 1.98-2.11 (m, 1H), 3.02 (brs, 1H), 4.40 (t, 1H, J=6.8 Hz), 7.18-7.55 (m, 5H). High mass calcd for $C_{21}H_{31}NO$: 313.2406, Obsd: 313.2379.

Removal of the Chiral Auxiliary.

Boc-(S)-dolaphenine (22). To a stirred solution of hydroxylamine hydrochloride (164 mg, 2.29 mmol) in ethanol at room temperature was added $AcONa{\cdot}3H_2O$ (311 mg, 2.29 mmol) and then dropwise **19a** (270 mg, 0.76 mmol) in ethanol (2 ml). The mixture was stirred at room temperature. After the solvent was concentrated *in vacuo*, benzene (30 ml) was added. The benzene solution was washed with saturated aqueous $NaHCO_3$ (10 ml) and saturated aqueous NaCl (10 ml). After the benzene was evaporated, 5% aqueous HCl (10 ml) was added. The mixture was stirred for 0.5 h, and extracted with Et_2O (30 ml). The aqueous layer was basified with $NaHCO_3$ and extracted with Et_2O (30 ml × 2). The extracts were dried over K_2CO_3 and concentrated *in vacuo*. The residue was dissolved in dioxane (1 ml), and Boc_2O (280 mg, 1.282 mmol) in dioxane (2 ml) was added at 0°C. The mixture was stirred at room temperature and diluted with water (20 ml). The mixture was extracted with Et_2O (30 ml × 2). The extracts were washed with saturated aqueous NaCl (20 ml) and dried over Na_2SO_4. Concentration *in vacuo* gave a colorless oil, which was purified by silica gel column chromatography with benzene-Et_2O (6:1) to give Boc-(S)-dolaphenine (**22**, 186 mg, 80%), identified with the authentic sample.[9]

(S)-N-Boc-1-(2-furyl)-2-phenylethylamine (27b). Purified by silica gel column chromatography with hexane-Et_2O (5:1), a white solid, mp 72-73°, $[\alpha]_D^{26.5}$ -35.2° (c 1.01, $CHCl_3$). IR ν_{max} (nujol): 3366, 2855, 1690, 1516, 1454, 1173, 729, 702 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.45 (s, 9H), 3.16 (d, 2H, J=6.6Hz), 4.89 (br, 1H, disappeared with D_2O), 5.06 (br, 1H), 6.06 (d, 1H, J=3.3Hz), 6.30 (dd, 1H, J=3.3, 1.8Hz), 7.03-7.37 (m, 5H), 7.41 (dd, 1H, J=0.8, 1.8Hz). Anal. calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.31; N, 4.87. Found; C, 70.95; H, 7.46; N, 4.68.

(S)-N-Boc-1,2-diphenylethylamine (27c). Purified by silica gel column chromatography with hexane-Et_2O (5:1), a white solid, mp 107-110°, $[\alpha]_D^{25}$ -3.15° (c 0.5, $CHCl_3$). IR ν_{max} (nujol): 3393, 2855, 1687, 1516, 1173, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.31 (s, 9H), 2.82-3.20 (m, 2H), 4.70 (br, 1H), 4.80-4.90 (br, 1H), 6.87-7.32 (m, 10H). Anal. calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.79; N, 4.71. Found: C, 76.95; H; 7.89; N, 4.43.

(S)-N-Boc-2-phenyl-1-(2-pyridyl)ethylamine (27d). Purified by silica gel column chromatography with hexane-ethyl acetate (3:1), a white solid, mp 60-61.5°, $[\alpha]_D^{26.5}$ +13.2° (c, 0.98, $CHCl_3$). IR ν_{max} (nujol): 3382, 2926, 1682, 1516, 1171, 779, 752, 735 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.43 (s, 9H), 3.05 (dd, 1H, J=13.0, 7.7Hz),3.09-3.24 (m, 1H), 4.97 (d, 1H, J=6.6Hz), 5.76 (br, 1H), 6.85-7.72 (m, 7H), 7.50 (t, 1H, J=7.0Hz), 8.57 (d, 1H, J=4.3Hz). Anal. calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.18; H, 7.44; N, 9.38.

(S)-Boc-2-phenyl-1-(2-thienyl)ethylamine (27a) and (-)-3-Hydroxy-2-caranone Oxime (21b). To a stirred solution of hydroxylamine hydrochloride (100 mg, 1.39 mmol) in ethanol at room temperature was added $AcONa{\cdot}3H_2O$ (190 mg, 1.39 mmol) and then dropwise **26a** (161 mg, 0.455 mmol) in ethanol (2 ml). After being stirred at room temperature for 23 hr, the mixture was concentrated *in vacuo*, and benzene (40 ml) was added. The benzene solution was washed with saturated aqueous $NaHCO_3$ (10 ml) and saturated aqueous NaCl (10 ml). After the benzene was evaporated, 5% aqueous HCl (10 ml) was added. The mixture was stirred for 0.5 hr and extracted with Et_2O (30 ml). The extracts were dried over K_2CO_3 and concentration *in vacuo* gave a pale yellow solid, which was purified by silica gel chromatography with benzene-Et_2O (3:1) to give a white solid (68%). The solid was recrystallized to give pure (-)-3-hydroxy-2-caranone oxime (**21b**) as a colorless prism, mp 120-122°C (Et_2O-hexane), $[\alpha]_D^{25}$ -279.0 ° (c 0.50, $CHCl_3$). IR ν_{max} (nujol): 3372, 1628, 1375, 1307, 1144, 1119, 951, 912, 806 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.90 (s, 3H), 1.06-

1.12 (m, 1H), 1.19 (s, 3H), 1.41 and 1.38-1.49 (s and m, 4H), 1.57 (d, 1H, J=8.3 Hz), 1.60-1.79 (m, 2H), 1.8-2.1 (br, 1H, disappeared with D_2O), 2.07-2.27 (m, 1H), 7.20 (s, 1H, disappeared with D_2O). Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found; C, 65.30; H, 9.34; N, 7.48.

The aqueous layer was basified with $NaHCO_3$ and extracted with Et_2O (20 ml × 2). The extracts were dried over K_2CO_3 and concentrated *in vacuo*. The residue was dissolved in dioxane (0.5 ml), Boc_2O (170 mg, 0.78 mmol) in dioxane (1 ml) was added at 0°C. The mixture was stirred at room temperature and diluted with water (20 ml). The mixture was extracted with Et_2O (30 ml × 2). The extracts were washed with saturated aqueous NaCl (20 ml) and dried over Na_2SO_4. Concentration in vacuo gave a pale yellow oil, which was purified by silica gel column chromatography with hexane-Et_2O (6:1) to give **27a** (mg, 69%) as a white solid, mp 64-65°C, $[\alpha]_D^{25}$ -14.00° (c 0.505, $CHCl_3$). IR ν_{max} (nujol): 3413, 1701, 1470, 1368, 1167, 1119, 1073, 698 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.52 (s, 9H), 3.14 (d, 2H, J=6.9 Hz), 4.64-4.84 (m, 1H), 5.22 (br, 1H), 6.84-7.05 (m, 3H), 7.12-7.34 (m, 5H). MS m/z: 302 (M^+-1), 212 (M^+-CH_2Ph), 187, 156, 112, 91.

In a similar manner, the chiral auxiliary of the other substrates **19b**, **26b**, and **26c** was removed. The spectral and thin-layer chromatographic behavior of the N-Boc-amines was identical with that of the authentic sample prepared from **19a**, **24b**, and **24c**, respectively.

Determination of Enantiomeric Excess of 22 and 27

1) Preparation of Racemic 22 and 27. Prepared from the racemic pinanone **2** as described in the preparation of (S)-**22** and **27**.

ii) HPLC Method The Boc derivative **22** (1 mg), **27a** (3.7 mg), and **27b** (7.5 mg) were dissolved in isopropanol (0.25 ml), respectively, and 1 μl of each solution was subjected to HPLC analysis using chiral Opti-Pak TA column (i.d. 3.9 × 30 mm) with hexane-i-PrOH (80:1) as an eluant (flow rate, 1.0 ml/ min; chart speed, 2 mm/ min; detector UV 254 nm). Retention times were as follows: 14.78 min for (S)-**22**, 20.65 min for (R)-**22**; 14.15 min for (S)-**27a**, 22.3 min for (R)-**27a**; 9.65 min for (S)-**27b**, 14.70 min for (R)-**27b**.

iii) (R)-α-Methoxy-α-trifluoromethylphenylacetic Acid ((R)-MTPA) Amides of 27c and 27d. (R)-MTPA amides of **27c** and **27d** were prepared by the method reported by D. E. Ward and C. K. Rhee.[11] A mixture of **27d** (35 mg, 0.117 mmol) and 10% HCl-MeOH (1 ml) was stirred at room temperature for 2 h. Concentration *in vacuo* gave **27d**·HCl as a white solid. Oxalyl chloride (64 μl, 0.734 mmol) was added to a solution of (R)-(+)-MTPA (36 mg, 0.154 mmol) in hexane (5 ml) at room temperature. After 1h, the mixture was filtered and concentrated to give (R)-MTPACl. To a solution of (R)-MTPACl in CH_2Cl_2 (2 ml) was added dropwise **27d**·HCl in CH_2Cl_2 (3 ml) and then TEA (140 μl, 1.004 mmol) and DMAP (10 mg, 0.08 mmol) at 0°C. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 (30 ml). The organic layer was washed with saturated aqueous $NaHCO_3$ (10 ml), water (10 ml), and saturated aqueous NaCl (10 ml), and dried over Na_2SO_4. Concentration *in vacuo* gave the residue, which was purified by silica gel column chromatography with hexane-Et_2O to give a pale yellow oil (42 mg, 86%). The ^1H NMR spectrum of the MTPA amide of **27d** thus obtained was measured (JEOL EX-270 spectrometer) and the enantiomeric excess was determined from the ratio of integration of the corresponding peaks.

Deoximation of (-)-3-Hydroxy-2-caranone Oxime (21b). To NH_4OAc (550 mg, 6.92 mmol) in water (1.5 ml) was added 20% aqueous $TiCl_3$ (1 ml, 1.30 mmol) at 0°C. (-)-3-Hydroxy-2-caranone oxime (**21b**) (80 mg, 0.437 mmol) in dioxane (1.5 ml) was added, and the mixture was stirred at 0°C for 6 hr. The mixture was extracted with Et_2O (30 ml × 2) and the extracts were washed with saturated aqueous $NaHCO_3$ (20 ml) and saturated aqueous NaCl (20 ml), and dried over $MgSO_4$. The aqueous layer was acidified with aqueous 1N HCl and stirred at room temperature for 18 hr, and extracted with Et_2O (30 ml × 2). The extracts were washed with saturated aqueous $NaHCO_3$ (20 ml), and saturated aqueous NaCl (20 ml), and dried over $MgSO_4$. Concentration *in vacuo* afforded a colorless oil, which was purified by silica gel column chromatography with hexane-AcOEt (2:1) to give (-)-3-hydroxy-2-caranone ((-)-**2b**, 48 mg, 66%) as a colorless oil, whose optical rotations, spectral and thin-layer chromatographic behavior was indentical with that of (-)-**2b** prepared from (+)-2-carene (**11**).

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