SYNTHESIS OF (+)-PREUSSIN

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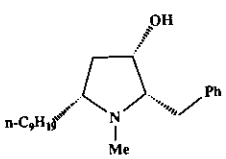
Abstract --- A total synthesis of (+)-preussin (1), a novel antifungal agent, was achieved via asymmetric 1,3-dipolar cycloaddition of decyl methyl nitrone (2) with (-)-1-phenyl-3-buten-2-ol (3) as a key reaction.

(+)-Preussin[1] (1) produced by the fermentation of Aspergillus ochraceus ATCC 22947 exhibits an antifungal activity and the absolute structure of this compound was determined as shown in Figure 1 by Johnson et al.[2]

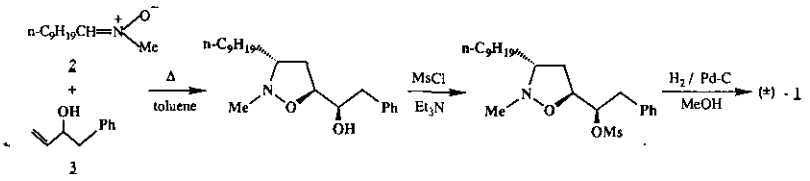
Figure 1



(+)-Preussin (1)

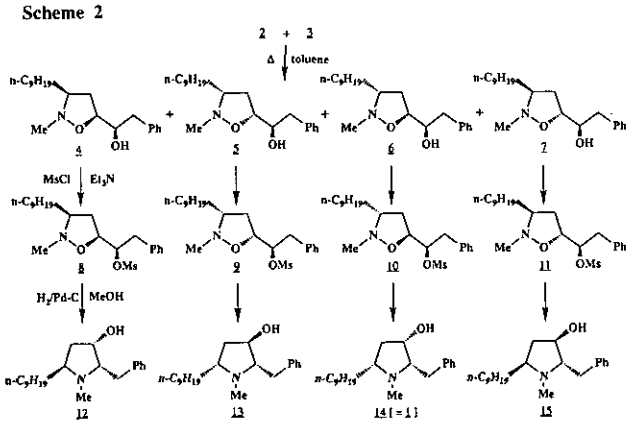
In 1991, Pak et al. reported the first asymmetric synthesis of 1 from D-glucose via 17 steps.[3] In recent years, a few reports regarding the asymmetric 1,3-dipolar cycloaddition using chiral dipolarophiles have been published.[4] Our synthesis of 1 described here is composed of 9 steps from D-phenylalanine via asymmetric 1,3-dipolar cycloaddition as a key reaction as described in Scheme 1.

Scheme 1



First, a synthesis of racemic preussin from decyl methyl nitrone (2) and dl-1-phenyl-3-buten-2-ol (3) was examined according to the procedure described in Scheme 1. Compounds 2 may exist as (Z)- and (E)-forms (ca. 1 : 1 on the basis of ^{1}H-nmr spectrum), which could not be separated from each other. The cycloaddition of 2 with 3 proceeded within 12 h under reflux in toluene to obtain a mixture of four diastereomeric adducts. Each of the products was isolated from the reaction mixture by silica gel column chromatography and the compounds (4-7) were eluted in order. These products were spectroscopically presumed to have the structures of 4-7 tentatively shown in Scheme 2. However, discrimination of the structures (4-7) could not be accomplished in this step because their ^{1}H-nmr spectra were complicated. Therefore, compounds (4-7) were respectively led to compounds (12-15) whose structures were determined spectroscopically. On the basis of the results, the structures of compounds (4-7) were clarified.

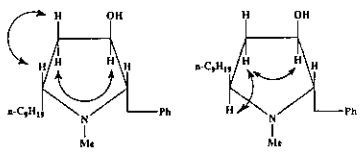
Scheme 2



Compounds (4-7) were mesylated to give (8-11) respectively, which were hydrogenolized in the presence of 10 % palladium on carbon. The amino group resulting from this reduction attacked the carbon attached the mesyloxy group by a intramolecular S_N2 reaction to give the corresponding pyrrolidine derivatives (12-15) (Scheme 2). The ^1H- and ^{13}C-nmr spectra of 14 prepared from 6 via 10 agreeded with reported data[1,3] of naturally occurring preussin (1). These data suggest that 6 is the target cycloadduct. The structures of 13 and 15 were determined by their ^1H-^1H NOESY based on NOE enhancement observed at the ^1H-^1H correlations described in Figure 2. On the basis of these NOE experiments, the structures of 5 and 7 were clarified. Accordingly, the structures of 12 and 4 were deductively determined.

Figure 2

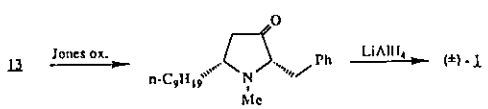
NOE enhancement



13 15

Compound (13) was subjected to Jones oxidation and the resulting ketone (16) was reduced with lithium aluminum hydride to obtain an alcohol whose spectroscopic data were identical with that of 14, namely 1. This result shows that a hydride anion attacks the carbonyl group with a facial selectivity. (Scheme 3)

Scheme 3

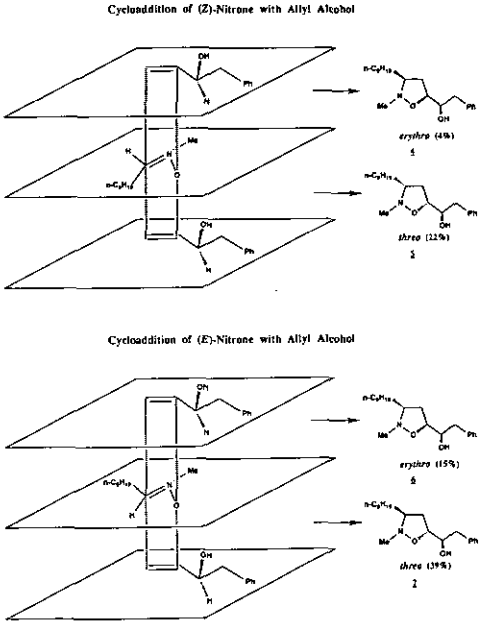


16

In the cycloaddition of the first step, 5 and 7 were the major products, and 4 and 6 were the minor products. It was presumed that there are four types of transition states between 2 and 3 in the cycloaddition step

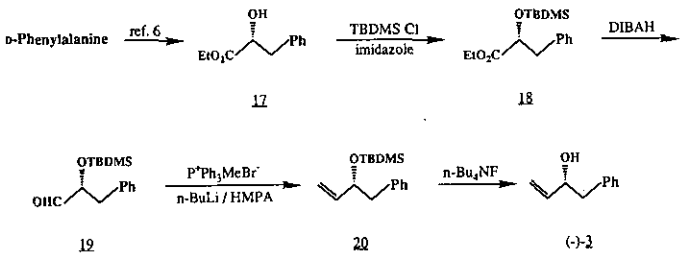
as illustrated in Figure 3. The previous results show that the structural correlation between their two oxygen atoms is threo in 5 and 7, and erythro in 4 and 6. Houk et al.[5] stated that the cycloaddition of nitrile oxides with allyl alcohols gave corresponding threo compounds slightly more than erythro ones. Our results accorded with their results.

Figure 3



On the basis of the synthesis of dl-1, (-)-3 was adopted for the synthesis of naturally occurring (+)-1. The dipolarophile (-)-3[7] was prepared according to the procedure described in Scheme 4.

Scheme 4



The cycloaddition of 2 with (-)-3 afforded four cycloadducts (+)-4 ($[\alpha]_D^{23}$= +63.5°, c = 1.0, $CHCl_3$), (-)-5 ($[\alpha]_D^{26}$= -101°), (-)-6 ($[\alpha]_D^{26}$= -60.5°) and (+)-7 ($[\alpha]_D^{26}$= +48.1°). The target compound, (+)-1, was obtained from (-)-6 *via* the mesyloxy derivative ((-)-10, $[\alpha]_D^{26}$=-34.6°) as a waxy solid whose optical rotation value ($[\alpha]_D^{26}$= +30.9°, c = 1.0, $CHCl_3$) was almost the same to the reported value of (+)-preussin; $[\alpha]_D^{25}$= +22.0° (natural[1]), +31.08° (synthetic[3]).

EXPERIMENTAL

The melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. ^{1}H-Nmr spectral data were recorded on a Varian Gemini 300 or a Brucker AM-400 in $CDCl_3$ using TMS as the internal standard. Optical rotations were measured with a Japan Spectroscopic Co. DIP-360 automatic polarimeter. Ir spectra were recorded with a Japan Spectroscopic Co. A-100. Mass spectra were taken with a Hitachi M-80B Mass Spectrometer. Column chromatography was conducted on Wakogel C-200 (Silica gel, 100-200 mesh), and medium pressure column chromatography was carried out using a UVILOG ALPC-100 as the pump, UVILOG 5IIIa as the UV detector (Oyo Bunko KiKi Co., Ltd., Tokyo) and Kiesel gel 60 (230-400 mesh, Merck AG, Darmstadt) as the packing material.

N-Decanylidenemethylamine *N*-Oxide (2): After stirring a mixture of *N*-methylhydroxylamine hydrochloride (6.1 g, 73 mmol) and Na_2CO_3 (10.7 g, 101 mmol) in tetrahydrofuran (THF) (60 ml) at room temperature for 1 h, decanal (11.4 g, 73 mmol) was added dropwise to this mixture. The whole was stirred further overnight. The resulting precipitates were filtered off and the filtrate was evaporated *in vacuo* to afford 2 (12.4 g, 92 %) as a colorless solid.

Colorless prisms; mp 58-60°C (hexane); ms: *m/z* 185 (M^+); ^{1}H-nmr (400 MHz): δ 0.88 (3H, t, J = 6.8 Hz), 1.26-1.36 (12H, m), 1.47-1.55 (2H,

m, J = 7.3 Hz), 2.48 and 2.49 (2H, dt, J = 6.2 and 7.4 Hz), 3.680 and 3.683 (3H, s), 6.655 and 6.657 (1H, t, J = 5.8 Hz). Anal. Calcd for $C_{11}H_{23}NO$: C, 71.30; H, 12.51; N, 7.56. Found: C, 70.93; H, 12.33; N, 7.62.

2-Methyl-5-(1-hydroxy-2-phenylethyl)-3-nonylisoxazolidines (4-7):

A mixture of 2 (190 mg, 1.0 mmol) and 3 (150 mg, 1.0 mmol) was refluxed in toluene (4 ml) for 12 h. After removing the solvent by distillation in vacuo, the chromatographic separation of the oily residue was carried out on a silica gel column using a mixture of hexane and Et_2O (7 : 3) as the developing solvent. Compounds (4, 5, 6 and 7) were eluted in order and their yields were 4 %, 22 %, 15 % and 39 %, respectively. These products could not be distilled.

4: Colorless oil; ms: m/z 333 (M^+); ir (neat): 3400 (ν_{OH}) cm^{-1}; ^1H-nmr (400 MHz): δ 0.89 (3H, t, J = 6.8 Hz), 1.28-1.53 (17H, m), 2.09-2.17 (1H, m), 2.35-2.42 (1H, m), 2.49 (1H, br s), 2.62 (3H, s), 2.65 (1H, dd, J = 6.7 and 13.6 Hz), 2.77 (1H, dd, J = 7.5 and 13.6 Hz), 3.97 (1H, ddd, J = 3.0, 5.5 and 8.4 Hz), 4.17 (1H, ddd, J = 3.0, 7.5 and 13.6 Hz), 7.19-7.31 (5H, m). High resolution ms: Calcd for $C_{21}H_{35}NO_2$: 333.2668. Found: 333.2653.

5: Colorless oil; ms: m/z 333 (M^+); ir (neat): 3375 (ν_{OH}) cm^{-1}; ^1H-nmr (400 MHz): δ 0.88 (3H, t, J = 6.9 Hz), 1.26-1.58 (16H, m), 1.88-1.95 (1H, m), 2.40-2.46 (3H, m), 2.65 (3H, s), 2.85 (1H, dd, J = 6.6 and 13.8 Hz), 2.91 (1H, dd, J = 7.0 and 13.8 Hz), 3.61-3.71 (1H, m), 3.94-3.98 (1H, m), 7.18-7.30 (5H, m). Anal. Calcd for $C_{21}H_{35}NO_2$: C, 75.63; H, 10.58; N, 4.20. Found: C, 75.60; H,10.72; N, 4.20.

6: Colorless oil; ms: m/z 333 (M^+). ir (neat): 3375 (ν_{OH}) cm^{-1}; ^1H-nmr (400 MHz): δ 0.89 (3H, t, J = 6.8 Hz), 1.27-1.34 (17H, m), 1.49-1.59 (3H, m), 1.90 (1H, dd, J = 3.6 and 8.4 Hz), 2.43 (1H, br s), 2.67 (3H, s), 2.75-2.77 (1H, m), 3.96-4.00 (1H, m), 7.21-7.32 (5H, m). High

resolution ms: Calcd for $C_{21}H_{35}NO_2$: 333.2668. Found: 333.2661.

7: Colorless oil; ms: m/z 333 (M^+); ir (neat): 3380 (ν_{OH}) cm^{-1}; ^{1}H-nmr (400 MHz): δ 0.88 (3H, t, J = 6.8 Hz), 1.27-1.34 (12H, m), 1.45-1.62 (4H, m), 1.90-1.97 (1H, m), 2.00-2.12 (1H, m), 2.17-2.23 (1H, m), 2.47 (1H, br s), 2.69 (3H, s), 2.82 (2H, d, J = 6.6 Hz), 3.70-3.77 (1H, m), 3.95-4.04 (1H, m), 7.20-7.32 (5H, m). Anal. Calcd for $C_{21}H_{35}NO_2$: C, 75.63; H, 10.58; N, 4.20. Found: C, 75.35; H, 10.64; N, 4.18.

General Procedure for the Preparation of 2-Methyl-5-(1-mesyloxy-2-phenylethyl)-3-nonylisoxazolidines (8-11): Et_3N (3.3 ml, 24 mmol) and MsCl (0.46 ml, 6 mmol) were added successively at -15°C to the solution of 4-7 (1.0 g, 3 mmol) in dry CH_2Cl_2 (25 ml). After stirring for 30 min at the same temperature and 1 h under cooling on an ice-water bath, the mixture was poured into water (25 ml) and extracted with CH_2Cl_2 (25 ml X 3). The CH_2Cl_2 extract was washed with saturated $NaHCO_3$ (75 ml X 1) and dried over Na_2SO_4. The solvent was removed by distillation to afford the desired compounds (8-11), which were purified by silica gel column chromatography using a mixture of hexane and AcOEt (4 : 1) as the developing solvent. These products could not be distilled.

8: Colorless oil; yield: 74 %; ms: m/z 411 (M^+). ir (neat): 1345, 1170 (ν_{SO}) cm^{-1}; ^{1}H-nmr (300 MHz): δ 0.88 (3H, t, J = 6.8 Hz), 1.27-1.43 (13H, m), 1.50-1.60 (3H, m), 2.06 (1H, dt, J = 12.3, 7.7 Hz), 2.44-2.53 (2H, m), 2.60 (3H, s), 2.63 (3H, s), 3.00 (1H, dd, J = 7.7 and 14.3 Hz), 3.13 (1H, dd, J = 5.4 and 14.3 Hz), 4.15 (1H, dd, J = 7.7 and 13.0 Hz), 4.90 (1H, dt, J = 7.7 and 5.4 Hz), 7.25-7.35 (5H, m). High resolution ms: Calcd for $C_{22}H_{37}NO_4S$: 411.2443. Found: 411.2449.

9: Colorless oil; yield: 99 %; ms: m/z 411 (M^+); ir (neat) : 1340, 1165 (ν_{SO}) cm^{-1}; ^{1}H-nmr (400 MHz): δ 0.89 (3H, t, J = 6.8 Hz), 1.24-1.31 (12H, m), 1.55-1.58 (3H, m), 1.73-1.80 (1H, m), 2.44-2.58 (3H, m), 2.61 (3H, s), 2.76 (3H, s), 2.92 (1H, dd, J = 7.1 and 14.5 Hz), 3.14 (1H, dd,

J = 4.6 and 14.5 Hz), 4.13 (1H, dd, J = 7.1 and 14.9 Hz), 4.84 (1H, dt, J = 4.6 and 7.1 Hz), 7.23-7.34 (5H, m). Anal. Calcd for $C_{22}H_{37}NO_4S$: C, 64.20; H, 9.06; N, 3.40. Found: C, 64.05; H, 9.21; N, 3.44.

10: Colorless oil; yield: 96 %; ms: m/z 411 (M^+); ir (neat): 1350, 1170 (ν_{SO}) cm^{-1}; ^{1}H-nmr (400 MHz): δ 0.89 (3H, t, J = 6.8 Hz), 1.27-1.43 (14H, m), 1.44-1.63 (2H, m), 1.99 (1H, dt, J = 12.1 and 8.7 Hz), 2.41-2.46 (1H, m), 2.47-2.55 (1H, m), 2.61 (3H, s), 2.69 (3H, s), 3.02 (2H, d, J = 6.4 Hz), 4.03-4.14 (1H, m), 4.89 (1H, dt, J = 4.1 and 6.7 Hz), 7.23-7.34 (5H, m). High resolution ms: Calcd for $C_{22}H_{37}NO_4S$: 411.2443. Found: 411.2426.

11: Colorless oil; yield: 94 %; ms: m/z 411 (M^+); ir (neat) : 1340, 1160 (ν_{SO}) cm^{-1}; ^{1}H-nmr (400 MHz): δ 0.88 (3H, t, J = 6.8 Hz), 1.20-1.32 (14H, m), 1.53-1.58 (3H, m), 1.98-2.05 (1H, m), 2.26-2.32 (1H, m), 2.61 (3H, s), 2.70 (3H, s), 3.02 (1H, dd, J = 8.3 and 14.2 Hz), 3.10 (1H, dd, J = 5.1 and 14.2 Hz), 4.14 (1H, br s), 4.84 (1H, dt, J = 8.3 and 5.1 Hz), 7.24-7.34 (5H, m). Anal. Calcd for $C_{22}H_{37}NO_4S$: C, 64.20; H, 9.06; N, 3.40. Found: C, 64.15; H, 9.25; N, 3.44.

General Procedure for the Preparation 1-Methyl-5-nonyl-2-phenylmethyl-3-hydroxypyrrolidines (12-15): A solution of 8-11 (1.2 g, 3 mmol) in MeOH (25 ml) was shaken in H_2 stream at room temperature over 10 % Pd-C (600 mg). After hydrogen absorption had ceased, the catalyst was filtered off and the filtrate was evaporated under reduced pressure. The residue was extracted with $CHCl_3$ (30 ml) and the extract was washed with saturated $NaHCO_3$ (30 ml) and dried over Na_2SO_4. The solvent was removed by distillation under reduced pressure and the residue was applied on medium-pressure column chromatography using a mixture of CH_2Cl_2 and MeOH (19 : 1) as the developing solvent to obtain 12-15.

12: Colorless viscous oil; yield: 49 %; ms: m/z 317 (M^+); ir (neat): 3280 (ν_{OH}) cm^{-1}; ^{1}H-nmr (400 MHz): δ 0.88 (3H, t, J = 6.8 Hz), 1.26-1.43 (16H, m), 1.76-1.82 (2H, m), 2.17-2.23 (1H, m), 2.68 (3H, s), 3.02 (1H, dd, J = 4.4 and 13.0 Hz), 3.14 (1H, dd, J = 10.5 and 13.0 Hz), 3.24-3.46 (1H, m), 3.61 (1H, m), 4.10 (1H, m), 7.21-7.34 (5H, m). High resolution ms: Calcd for $C_{21}H_{35}NO$: 317.2719. Found: 317.2726.

13: Colorless waxy solid; mp 37-39°C; yield: 61 %; ms: m/z 317 (M^+); ir (KBr): 3100 (ν_{OH}) cm^{-1}; ^{1}H-nmr (400 MHz): δ 0.88 (3H, t, J = 6.8 Hz), 1.16-1.33 (12H, m), 1.57 (5H, br s), 1.61-1.71 (1H, m), 1.74 (1H, dd, J = 6.7 and 13.3 Hz), 2.35 (3H, s), 2.39-2.47 (2H, m), 2.56 (1H, dd, J = 9.4 and 13.3 Hz), 3.05 (1H, dd, J = 4.5 and 13.3 Hz), 3.99-4.03 (1H, m), 7.19-7.32 (5H, m). Anal. Calcd for $C_{21}H_{35}NO$: C, 79.44; H, 11.11; N, 4.41. Found: C, 79.06; H, 11.25; N, 4.41.

14: Colorless waxy solid; yield: 69 %. The spectral (^{1}H- and ^{13}C-nmr, ms, ir) data agreed with the reported data[1,3]. Anal. Calcd for $C_{21}H_{35}NO$: C, 79.44; H, 11.11; N, 4.41. Found: C, 79.53; H, 10.91; N, 4.50.

15: Colorless syrup; yield: 68 %; ms: m/z 316 (M^+-1); ir (neat): 3320 (ν_{OH}) cm^{-1}; ^{1}H-nmr (400 MHz): δ 0.88 (3H, t, J = 6.8 Hz), 1.21-1.31 (16H, m), 1.53 (1H, dd, J = 4.9 and 14.2 Hz), 1.54-1.72 (1H, m), 2.21 (1H, dd, J = 10.7 and 13.4 Hz), 2.34-2.41 (1H, m), 2.46 (3H, s), 2.65-2.69 (1H, m), 2.97 (1H, dd, J = 4.2 and 13.4 Hz), 3.17 (1H, dd, J = 4.2 and 10.7 Hz), 3.91 (1H, d, J = 6.4 Hz), 7.13-7.33 (5H, m). High resolution ms: Calcd for $C_{21}H_{34}NO$ (M^+-H): 316.2640. Found: 316.2640.

1-Methyl-5-nonyl-2-phenylmethyl-3-oxopyrrolidine (16): Jones reagent, prepared from CrO_3 (520 mg, 5.2 mmol), distilled water (1.5 ml) and c. H_2SO_4 (0.51 ml), was added dropwise to a solution of 13 (530 mg, 1.7 mmol) in acetone (11 ml) under cooling on an ice-water bath. After stirring for 5 h, brine (10 ml) was added to the mixture, which was

extracted with $CHCl_3$ (20 ml X 3). The organic layer was washed with saturated $NaHCO_3$ (50 ml) and dried over Na_2SO_4. The solvent was removed by distillation under reduced pressure to obtain a brownish oil, which was purified by medium-pressure column chromatography using a mixture of hexane and AcOEt (9 : 1) as the developing solvent to afford 16 (390 mg, 74 % yield) as a yellow oil. Compound (16) could not be distilled. Yellow oil; ms: m/z 315 (M^+); ir (neat): 1755 (ν_{CO}) cm^{-1}; ^1H-nmr (400 MHz): δ 0.88 (3H, t, J = 6.8 Hz), 1.14-1.31 (16H, m), 1.77 (1H, dd, J = 10.7 and 17.8 Hz), 2.31 (3H, s), 2.38 (1H, dd, J = 6.1 and 17.8 Hz), 2.44-2.51 (1H, m), 2.75 (1H, t, J = 5.0 Hz), 2.85 (1H, dd, J = 5.0 and 14.3 Hz), 3.05 (1H, dd, J = 4.7 and 14.3 Hz), 7.15-7.26 (5H, m). High resolution ms: Calcd for $C_{21}H_{33}NO$: 315.2562. Found: 315.2536.

Reduction of 1-Methyl-5-nonyl-2-phenylmethyl-3-oxopyrrolidine (16): $LiAlH_4$ (71.3 mg, 1.9 mmol) was added to a solution of 16 (221 mg, 0.7 mmol) in dry THF (8 ml) under cooling on an ice-water bath. After stirring for 30 min at room temperature, the reaction was quenched by addition of water (5 ml). The reaction mixture was filtered off through Celite (Wako Pure Chemical Industries, LTD.) and the solvent was removed by distillation in vacuo. The residue was extracted with $CHCl_3$ (10 ml X 3). The extract was washed with water (30 ml) and dried over Na_2SO_4. The solvent was removed by distillation under reduced pressure to afford a pale yellow solid, which was purified by silica gel column chromatography using a mixture of CH_2Cl_2 and MeOH (19 : 1) as the developing solvent to afford 1 (222 mg, 100 %) as a colorless waxy solid. The spectral (^1H- and ^{13}C-nmr, ms, ir) data agreed with the reported data.[1,3]

Ethyl 2-tert-Butyldimethylsilyloxy-3-phenylpropionate (18): A solution of 17[6] (12.7 g, 66 mmol) in dry DMF (50 ml) was added to a solution of tert-butyldimethylsilyl chloride (12 g, 80 mmol) and imidazole (5.4 g,

79 mmol) in dry DMF (200 ml). After being stirred overnight at room temperature, the reaction mixture was poured into water (250 ml) and extracted with Et_2O (250 ml X 3). The organic layer was washed with brine (500 ml) and water (500 ml), successively. After being dried over Na_2SO_4, the solvent was removed by distillation to afford an oily residue, which was purified by silica gel column chromatography using a mixture of hexane and AcOEt (4 : 1) as the developing solvent to afford 18 (19 g, 93 %) as a colorless oil.

Colorless oil; bp 118-122°C/3 torr (oil bath temp.); ms (CI) m/z: 309 (M^++1); ir (neat): 1760 (ν_{CO}) cm^{-1}; $[\alpha]_D^{28}$= +34.8° (c = 1.0, $CHCl_3$); ^{1}H-nmr (300 MHz): δ 0.01 (3H, s), 0.10 (3H, s), 1.01 (9H, s), 1.48 (3H, t, J = 7.1 Hz), 3.10 (1H, dd, J = 9.0 and 13.3 Hz), 3.30 (1H, dd, J = 3.9 and 13.3 Hz), 4.40 (2H, q, J = 7.1 Hz) and 4.41 (2H, q, J = 7.2 Hz), 4.54 (1H, dd, J = 3.9 and 9.0 Hz), 7.43-7.53 (m, 5H). Anal. Calcd for $C_{17}H_{28}O_3Si$: C, 66.19; H, 9.15. Found: C, 66.34; H, 9.15.

2-tert-Butyldimethylsilyloxy-3-phenylpropanal (19): DIBAH (36 ml of a 1 M solution in hexane, 36 mmol) was added dropwise to a solution of 18 (9.2 g, 30 mmol) in dry toluene (230 ml) over 15 min at -78°C under Ar stream. After being stirred for 3 h, the reaction was quenched by addition of water (2 ml). The reaction mixture was filtered off through Celite (Wako Pure Chemical Industries, LTD.) and the solvent was removed by distillation in vacuo. The residue was extracted with Et_2O (50 ml X 3). The extract was washed with water (100 ml) and dried over Na_2SO_4. The solvent was removed by distillation to afford an oily redidue, which was purified by silica gel column chromatography using a mixture of hexane and AcOEt (9 : 1) as the developing solvent to afford 19 (7.7 g, 97 %) as a colorless oil.

Colorless oil; bp 95-98°C/2 torr (oil bath temp.); ms (CI): m/z 265 (M^++1); ir (neat): 1760 (ν_{CO}) cm^{-1}; $[\alpha]_D^{28}$= +62.4° (c = 1.0, $CHCl_3$); ^{1}H-nmr (300 MHz): δ 0.07 (3H, s), 0.14 (3H, s), 1.08 (9H, s), 3.03 (1H, dd, J = 9.0 and 13.6 Hz), 3.25 (1H, dd, J = 4.0 and 13.6 Hz), 4.38 (1H, ddd, J = 1.7, 4.0 and 9.0 Hz), 7.45-7.56 (5H, m), 9.90 (1H, d, J = 1.7 Hz). Anal. Calcd for $C_{15}H_{24}O_2Si$: C, 68.13; H, 9.15. Found: C, 67.84; H, 8.98.

2-tert-Butyldimethylsilyloxy-1-phenyl-3-butene (20): Dry HMPA (3 ml) and BuLi (3.6 ml of 1.6 M solution in hexane, 5.7 mmol) were added successively to a stirred suspension of methyltriphenylphosphonium bromide (2 g, 5.6 mmol) in dry THF (17 ml) at -78°C under Ar stream. The mixture was stirred for 15 min at the same temperature and a further 30 min at 0°C. A solution of 19 (1 g, 3.8 mmol) in dry THF (13 ml) was added dropwise to the resulting solution over 15 min at -78°C. The mixture was stirred for 30 min at -78°C and further overnight at room temperature. The reaction was quenched by addition of water (10 ml) and the solvent was removed by distillation under reduced pressure. The residue was extracted with Et_2O (150 ml X 3) and the Et_2O extract was washed with brine (300 ml) and water (300 ml). After drying over Na_2SO_4, the solvent was removed by distillation to afford an oily residue, which was purified by silica gel column chromatography using a mixture of hexane and AcOEt (99 : 1) as the developing solvent to afford 20 (410 mg, 41 %) as a colorless oil.

Colorless oil; bp 84-88°C/3 torr (oil bath temp.); ms: m/z 262 (M^+); $[\alpha]_D^{28}$= +7.8° (c = 1.0, $CHCl_3$); ^{1}H-nmr (400 MHz): δ 0.007 (3H, s), 0.12 (3H, s), 1.06 (9H, s), 2.980 (1H, d, J = 7.1 Hz), 2.981 (1H, d, J = 5.8 Hz), 4.48 (1H, dt, J = 7.1 and 5.8 Hz), 5.25 (1H, dd, J = 1.5 and 10.4 Hz), 5.37 (1H, dd, J = 1.5 and 17.1 Hz), 6.08 (1H, ddd, J = 5.8, 10.4 and 17.1 Hz), 7.38-7.52 (5H, m). High resolution ms: Calcd for $C_{15}H_{23}OSi$

(M^+-CH_3): 247.1518. Found: 247.1520.

(-)-1-Phenyl-3-buten-2-ol (3): Bu_4NF (3.0 ml of 1.0 M solution in THF, 3 mmol) was added to a solution of 20 (405 mg, 1.5 mmol) in THF (6 ml) and the mixture was stirred for 15 h at room temperature. The solvent was removed by distillation under reduced pressure and then the residue was extracted with Et_2O (50 ml). The extract was washed with water (50 ml) and brine (50 ml), successively. After drying over Na_2SO_4, the solvent was evaporated to afford an oily residue, which was purified by column chromatography on silica gel using a mixture of hexane and AcOEt (9 : 1) as the developing solvent to afford (-)-3 (227 mg, 99 %) as a colorless oil. bp 88-94°C/3 torr; $[\alpha]_D^{27}$ = -11.4° (c = 1.0, CH_3OH). [$[\alpha]_D^{21}$= +9.4°[7] for (+)-3]

Asymmetric Synthesis of (+)-Preussin (1) via the Cycloaddition of 2 and (-)-3: Preparation of (+)-1 was carried out by using (-)-3 as the starting material according to the procedure for the synthesis of dl-1. Optical rotations of the intermediates (4-7, 10) were measured in $CHCl_3$ (c = 1.0) and the values are as follows:

(+)-4: $[\alpha]_D^{23}$= +63.5°; (-)-5: $[\alpha]_D^{26}$= -101°; (-)-6: $[\alpha]_D^{26}$= -60.5°; (+)-7: $[\alpha]_D^{26}$= +48.1°; (-)-10: $[\alpha]_D^{26}$= -34.6°.

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Received, 12th February, 1993