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A Total Synthesis of (−)-Antirhine

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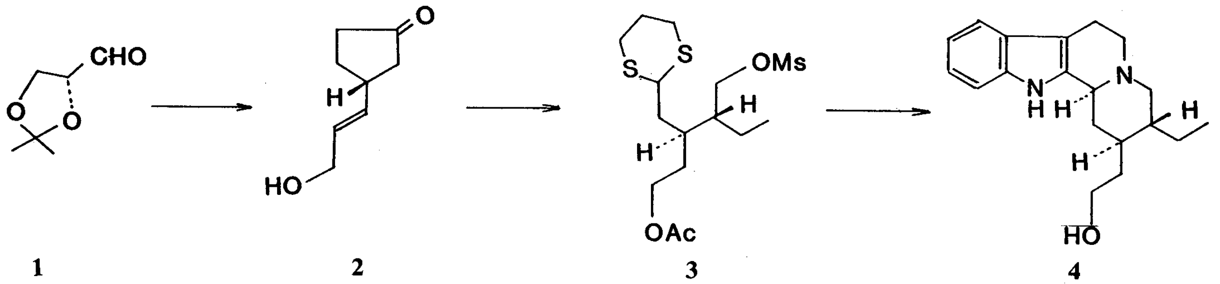
Total synthesis of (−)-antirhine (**5**) has been achieved from a potentially useful chiral synthon, (3*R*)-[3-hydroxy-(*E*)-prop-1-enyl]cyclopentanone (**2**) [derived from (*R*)-1,2-isopropylideneglyceraldehyde (**1**)], *via* the β,γ-unsaturated aldehyde (**12**), which was obtained by mild hydrolysis of the α-cyano-*N*,*N*-dimethylaminocyclopentanone (**11**).

Keywords——total synthesis; (−)-antirhine; optically active natural product; chiral synthon; (*R*)-1,2-isopropylideneglyceraldehyde

In a recent development in the total synthesis of optically active natural products, (*R*)-1,2-isopropylideneglyceraldehyde (**1**)[1] has been used as a chiral starting material for a number of biologically active compounds such as prostaglandins,[2] brefeldin A,[3] ipsdienol,[4] pestalotin,[5] leucotriene A_4,[6] and antirhine.[7] Recently, we reported the enantioselective total synthesis of (−)-dihydrocorynantheol (**4**)[8] *via* **3** using a potentially versatile chiral synthon, (3*R*)-[3-hydroxy-(*E*)-prop-1-enyl]cyclopentanone (**2**),[9] derived from **1**.



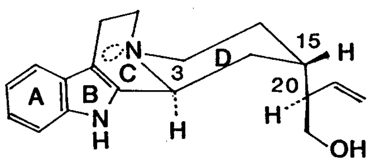
1 2 3 4

Chart 1

During our efforts toward the total synthesis of natural products employing carbohydrates as starting materials, we have been intrigued by the possibility of applying this chiral synthon (**2**) to the synthesis of (−)-antirhine (**5**)[10] possessing three chiral centers at C_3, C_{15}, C_{20}, although the total synthesis of **5** in both racemic[11] and optically active forms[7] had already appeared in recent publications. Antirhine (**5**), the major alkaloid of *Antirhea putaminosa*, is a unique *Corynanthe* variant with *cis* C/D ring juncture and has the less stable anti-relationship between the centers at C_3 and C_{15}.

It is well known that various types of indole alkaloids are biogenetically formed by a condensation of tryptamine and secologanin (**7**) derived from geraniol (**6**) as a non-tryptamine moiety.[12] Based on this fact, we chose **8** as a common intermediate leading to both secologanin (**7**) *via* **9** and antirhine (**5**).

In order to prepare the non-tryptamine moiety of natural antirhine (**5**), it is necessary to



5

Chart 2

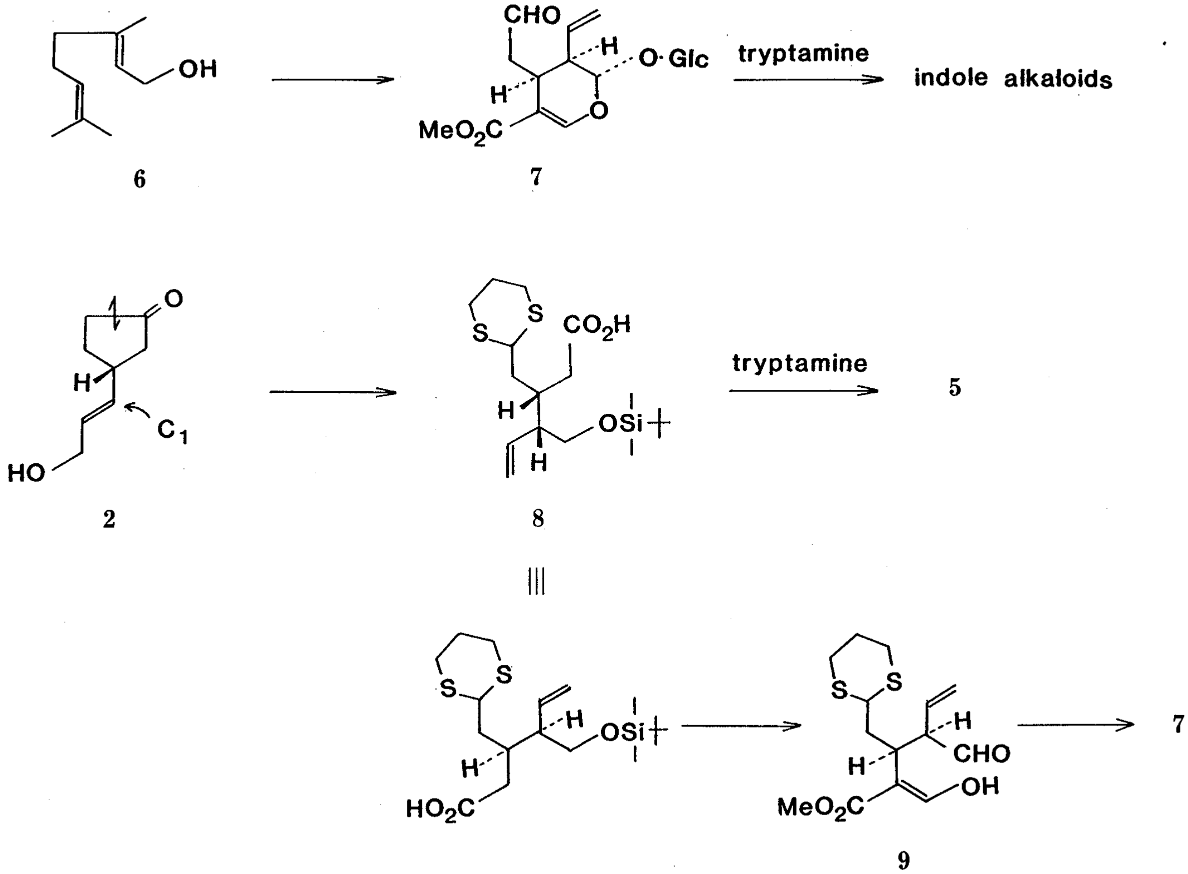


Chart 3

introduce one more carbon at C_1 in **2** and to cleave the cyclopentanone ring regioselectively as shown by the arrow (Chart 3). The former could be achieved by 2,3-sigmatropic rearrangement of the *N*,*N*-dimethylcyanomethylammonium bromide (**11**) derived from the allyl alcohol (**2**), whereas the latter was performed by the regioselective thioacetalization of the cyclopentanone (**2**) *via* the pyrrolidine enamine followed by basic cleavage according to the procedure developed by Marshall and Seitz.[13)]

We wish to report here a successful total synthesis of (−)-antirhine (**5**) from **2**.

The known cyclopentanone (**2**)[9)] was allowed to react with phosphorus tribromide in diethyl ether in the presence of pyridine at 0 °C to give the allylic bromide (**10**). The bromide (**10**) was converted, without purification, into the α-cyano-*N*,*N*-dimethylaminomethylcyclopentanone (**12**) *via* 2,3-sigmatropic rearrangement[14)] of the allylic ammonium bromide (**11**).[15)]

Hydrolysis of **12** with 30% aqueous oxalic acid in tetrahydrofuran (THF) provided the undesired α,β-unsaturated aldehyde (**14**) exclusively,[16)] whereas hydrolysis of **12** under mild conditions with cupric sulfate[17)] in ethanol at 80 °C for 10 min provided preferentially the desired β,γ-unsaturated aldehyde (**13**) in addition to **14** in a ratio of 9 : 1. High temperature and prolonged reaction time increased the yield of the undesired α,β-unsaturated aldehyde. Since attempts to selectively reduce the aldehyde group in the presence of the ketone group under various conditions resulted in failure, a somewhat circuitous route was adopted. Reduction of a mixture of **13** and **14** with sodium borohydride followed by protection of the resulting primary alcohol in **15** and **16** provided the *tert*-butyldimethylsilyl ether (**17**) and (**18**) as a separable mixture. Oxidation of **17** using pyridinium chlorochromate and sodium acetate in dichloromethane afforded the cyclopentanone (**19**) in 7% overall yield from **2**.

Regioselective dithioacetalization of **19** with trimethylene dithiotoluene-*p*-sulfonate[18] through the pyrrolidine enamine was performed to give the α-diketone monothioketal (**20**) in 70.4% yield. Basic cleavage[13] of **20** with potassium hydroxide in *tert*-butanol at 60 °C for 2 h produced the carboxylic acid (**21**) in 73.4% yield. Treatment of **21** with methyl chloroformate in the presence of triethylamine[19] gave the crude mixed anhydride (**22**), which on condensation with tryptamine in dichloromethane afforded the secondary amide (**23**), and the undesired amide (**24**) as an easily separable mixture in 80.8% yield, the formation ratio of the amides being 1 : 1.

Exposure of **23** to methyl iodide in aqueous acetonitrile[11,20] resulted in cyclization and simultaneous deprotection of the protecting group to give the lactam (**25**) in 64.5% yield. Finally, **25** was reduced with lithium aluminum hydride to afford (−)-antirhine (**5**),[21] mp 112—114 °C (lit.[10] 112—114 °C), $[\alpha]_D^{25}$ −1.9° (c=0.076, $CHCl_3$) (lit.[10] −2° (c=0.23, $CHCl_3$)), whose infrared (IR), proton nuclear magnetic resonance (^{1}H-NMR), and mass spectra (MS) and thin-layer chromatographic (TLC) behavior were identical with those of the authentic natural product, and (−)-C_3-*epi*-antirhine (**26**), in 50.6 and 22.6% yields, respectively.

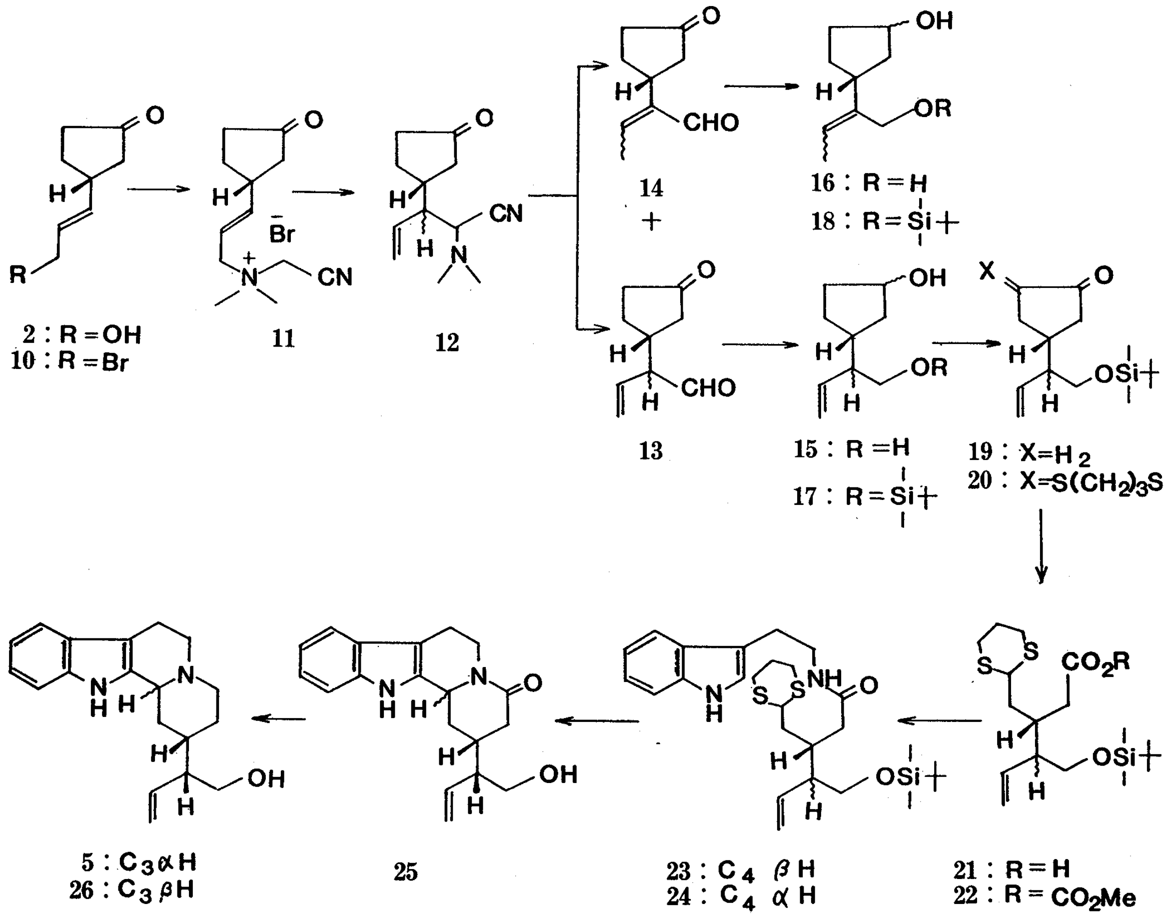


Chart 4

The predominant formation of natural antirhine (**5**) over *epi*-antirhine (**26**) may reflect a kinetic intramolecular Pictet–Spengler cyclization of the indolyl group to the imminium base from the less hindered β side, as shown in Chart 5.

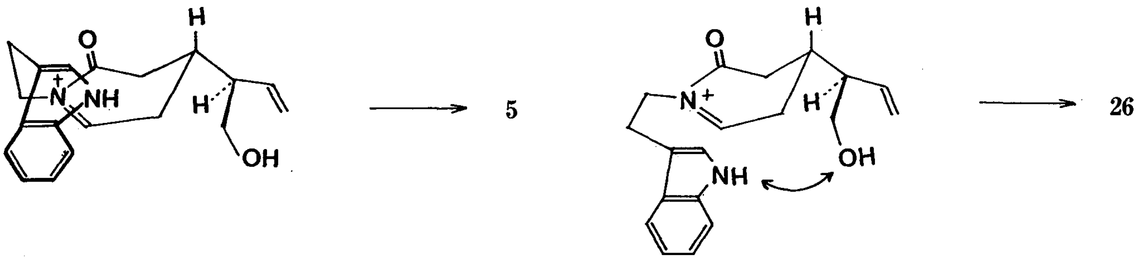


Chart 5

The transformation of (3*R*)-[3-hydroxy-(*E*)-prop-1-enyl]-cyclopentanone (**2**) into (−)-antirhine (**5**) has thus been achieved. Although the present report is limited to the synthesis of (−)-antirhine, **21** will undoubtedly serve as a chiral synthon for a large number of *Corynanthe*-type indole alkaloids, secologanin, semburine, and *epi*-semburine.

Experimental

The IR spectra were recorded on Shimadzu IR-400 and JASCO IR-810 spectrophotometers. MS were obtained with a JEOL-JMS-01-SG-2 spectrometer. The ^{1}H-NMR spectra were taken on JEOL JNM-PMX-60 and JEOL JNM-GX400 spectrometers in deuterochloroform with tetramethylsilane as an internal standard. Optical rotations were measured with a JASCO-DIP-4 automatic polarimeter. Melting points were measured on a Yazawa BY-1 micro melting point apparatus and are uncorrected.

(3*R*)-[3-Bromo-(*E*)-prop-1-enyl]cyclopentanone (10)——Phosphorus tribromide (6.83 g, 25.3 mmol) was added dropwise to a stirred solution of the allylic alcohol (**2**)$^{9)}$ (1.42 g, 10.1 mmol) and pyridine (200 mg, 2.53 mmol) in ether (30 ml) cooled with ice bath, and the mixture was stirred for 2 h at the same temperature. The mixture was diluted with ether, and washed with water and then brine. The extract was dried over magnesium sulfate and concentrated to give 2.01 g of the crude allylic bromide (**10**) as a pale yellow syrup, which was used in the next reaction without further purification. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}; 1730 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 3.93 (2H, dd, J=4, 2 Hz, CH_2Br), 5.10—6.13 (2H, m, CH=CH). High-MS for $C_8H_{11}BrO$ (M^+): Calcd *m/z* 201.9993, 203.9974. Found: 201.9983, 203.9954.

(3*R*)-[1-Formyl-prop-2-enyl]cyclopentanone (13)——The above crude allylic bromide (**10**) (2.01 g) in dimethyl sulfoxide (DMSO) (4 ml) was added dropwise to a stirred solution of dimethylaminoacetonitrile (916 mg, 10.9 mmol) in DMSO (3 ml) at room temperature under nitrogen and the mixture was stirred for 13 h to form the allylic ammonium bromide (**11**).

The above solution of **11** was added dropwise to a stirred solution of potassium *tert*-butoxide (1.39 g, 12.4 mmol) in THF (40 ml) at −10 °C under nitrogen and the mixture was stirred for 2 h at the same temperature. The reaction was quenched with saturated aqueous ammonium chloride and then the solvent was evaporated off to leave a residue, which was diluted with ether. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layer was washed with brine, dried over magnesium sulfate, and then evaporated to give the crude nitrile (**12**) (1.85 g) as a brown syrup which was used in the next reaction without further purification. High-MS for $C_{12}H_{18}N_2O$(M^+): Calcd *m/z* 206.1417. Found: 206.1410.

A mixture of the crude nitrile (**12**) (1.85 g, 9.88 mmol) and $CuSO_4 \cdot 5H_2O$ (2.22 g, 8.89 mmol) in ethanol (20 ml) was heated at 80 °C with stirring for 10 min under nitrogen. After the reaction was completed, the precipitate was filtered off. The filtrate was evaporated to leave a residue, which was extracted with ether. The extract was washed with brine, dried over magnesium sulfate, and concentrated to provide the crude aldehyde (549 mg) as a 9 : 1 mixture of the β,γ-unsaturated aldehyde (**13**) and the α,β-unsaturated aldehyde (**14**), which were characterized by ^{1}H-NMR. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1725 (C=O). ^{1}H-NMR ($CDCl_3$) δ: **13**: 4.92—5.62 (3.86H, m, $CH=CH_2$), 9.42 (0.9H, t, J=1 Hz, CHO). High-MS for $C_9H_{12}O_2$ (M^+): Calcd *m/z* 152.0836. Found: 152.0829. **14**: 6.53 (0.14H, q, J=7 Hz, C=CH), 9.17 (0.1H, d, J=2 Hz, CHO). This mixture was used in the next reaction without further purification because of its instability.

(3*R*)-(1-*tert*-Butyldimethylsilyloxymethylprop-2-enyl)cyclopentanol (17)——Sodium borohydride (273 mg, 7.22 mmol) was added to a stirred solution of the above crude aldehyde in methanol (4 ml) at 0 °C. The mixture was stirred for 1 h at room temperature, then the reaction was quenched with water and the whole was concentrated to leave a residue, which was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and then evaporated to provide a mixture of the diol (**15**) and (**16**) (396 mg) as a brown syrup, which was directly used in the next reaction without further purification. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3600—3200 (OH). MS *m/z*: 138 (M$^+$ − 18).

A solution of *tert*-butyldimethylsilyl chloride (306 mg, 2.03 mmol) in dimethylformamide (DMF) (3 ml) was added dropwise over 1 h to a stirred, cooled solution of the above crude diol (396 mg, 2.54 mmol) and imidazole (190 mg, 2.79 mmol) in DMF (3 ml) at −10 °C under nitrogen. The mixture was stirred for 3 h at −10 °C and the reaction was quenched with water. Evaporation of the solvent *in vacuo* left a residue, which was extracted with ether. The extract was washed with brine, dried over magnesium sulfate, and then evaporated to leave a residue as a colorless syrup, which was chromatographed on silica gel with 10% ethyl acetate–hexane as the eluent. The first elution with 10% ethyl acetate–hexane gave the undesired compound (**18**) (22 mg) as a colorless syrup. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3600—3200 (OH). ^{1}H-NMR (CDCl$_3$) δ: 0.08 (6H, s, SiMe$_2$), 0.92 (9H, s, Si^{t}Bu), 1.63 (3H, d, J = 7 Hz, Me), 4.07—4.28 (3H, m, CH$_2$Si, C$\underline{\mathrm{H}}$OH), 5.47 (1H, q, J = 7 Hz, C=CH). High-MS for $C_{15}H_{30}O_2Si$ (M$^+$): Calcd *m/z* 270.2013. Found: 270.2007. Further elution with the same solvent afforded the desired compound (**17**) (200 mg) (7.3% overall from **2**) as a colorless syrup. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3600—3200 (OH). ^{1}H-NMR (CDCl$_3$) δ: 0.03 (6H, s, SiMe$_2$), 0.87 (9H, s, Si^{t}Bu), 3.53 (2H, d, J = 6 Hz, CH$_2$OSi), 4.82 (1H, dd, J = 16, 2 Hz, CH=C$\underline{\mathrm{H}}_2$), 4.88 (1H, dd, J = 8, 2 Hz, CH=C$\underline{\mathrm{H}}_2$), 5.55, 5.57 (0.5H each, ddd each, J = 16, 8, 8 Hz, C$\underline{\mathrm{H}}$=CH$_2$). High-MS for $C_{11}H_{21}O_2Si$ (M$^+$ − 57): Calcd *m/z* 213.1309. Found: 213.1308.

(3*R*)-(1-*tert*-Butyldimethylsilyloxymethyl-prop-2-enyl)cyclopentanone (19)——A solution of the monoprotected alcohol (**17**) (130 mg, 0.484 mmol) in dichloromethane (2 ml) was added all at once to a suspension of pyridinium chlorochromate (209 mg, 0.968 mmol) and sodium acetate (79 mg, 0.968 mmol) in dichloromethane (8 ml), and the mixture was stirred for 1 h at room temperature. The mixture was filtered through a short silica gel pad and the filtrate was evaporated to leave a residue, which was purified by column chromatography on silica gel. Elution with 10% ethyl acetate–hexane provided the cyclopentanone (**19**) (123 mg, 95.3%) as a colorless syrup. $[\alpha]_D^{25}$ +66.0° (c = 1.254, CHCl$_3$) IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1730 (C=O). ^{1}H-NMR (CDCl$_3$) δ: 0.05 (6H, s, SiMe$_2$), 0.87 (9H, s, Si^{t}Bu), 3.60 (2H, d, J = 6 Hz, CH$_2$OSi), 4.95 (1H, dd, J = 16, 2 Hz, CH=C$\underline{\mathrm{H}}_2$), 5.02 (1H, dd, J = 8, 2 Hz, CH=C$\underline{\mathrm{H}}_2$), 5.50 (1H, ddd, J = 16, 8, 8 Hz, C$\underline{\mathrm{H}}$=CH$_2$). High-MS for $C_{15}H_{27}O_2Si$ (M$^+$ − 1): Calcd *m/z* 267.1780. Found: 267.1795.

(4*S*)-(*tert*-Butyldimethylsilyloxymethyl-prop-2-enyl)-2,2-(propane-1,3-dithio)cyclopentanone (20)——A mixture of the cyclopentanone (**19**) (351 mg, 1.31 mmol) and pyrrolidine (280 mg, 3.93 mmol) in dry benzene (10 ml) was refluxed with stirring for 7 h and water was removed azeotropically as it was formed. The mixture was concentrated to give the enamine, which was used in the next reaction without further purification.

A mixture of the crude enamine and trimethylene dithiotosylate (820 mg, 1.97 mmol) and triethylamine (332 mg, 3.28 mmol) in acetonitrile (20 ml) was stirred under reflux for 15 h. The solvent was evaporated off to leave a residue, which was extracted with chloroform. The extract was washed with brine, dried over magnesium sulfate, and then evaporated to leave a residue. The product was purified by column chromatography on silica gel. Elution with 10% ethyl acetate–hexane gave the thioketal (**20**) (341 mg, 70.4%) as a pale yellow syrup. $[\alpha]_D^{26}$ −46.4° (c = 0.625, CHCl$_3$). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1730 (C=O). ^{1}H-NMR (CDCl$_3$) δ: 0.03 (6H, s, SiMe$_2$), 0.87 (9H, s, Si^{t}Bu), 3.53 (2H, d, J = 6 Hz, CH$_2$OSi), 4.92 (1H, dd, J = 16, 2 Hz, CH=C$\underline{\mathrm{H}}_2$), 4.98 (1H, dd, J = 8, 2 Hz, CH=C$\underline{\mathrm{H}}_2$), 5.57, 5.60 (0.5H each, ddd each, J = 16, 8, 8 Hz, C$\underline{\mathrm{H}}$=CH$_2$). High-MS for $C_{18}H_{32}O_2S_2Si$ (M$^+$): Calcd *m/z* 372.1611. Found: 372.1598.

(3*S*)-(Propane-1,3-dithio)ethyl-4-*tert*-butyldimethylsilyloxymethyl-5-hexenoic Acid (21)——Powdered potassium hydroxide (54 mg, 0.966 mmol) was added to a solution of the thioketal (**20**) (102 mg, 0.276 mmol) in *tert*-butanol (5 ml) and the mixture was stirred for 2 h at 60 °C. The solvent was evaporated off to leave a residue, which was acidified with 1 N aqueous HCl and then extracted with ether. The organic layer was washed with brine, and dried over magnesium sulfate. The solvent was evaporated off to leave a residue, which was subjected to chromatography on silica gel. Elution with chloroform yielded the carboxylic acid (**21**) (78.6 mg, 73.4%) as a pale yellow syrup. $[\alpha]_D^{26}$ +2.6° (c = 0.453, CHCl$_3$). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1700 (CO$_2$H), ^{1}H-NMR (CDCl$_3$) δ: 0.03 (6H, s, SiMe$_2$), 0.87 (9H, s, Si^{t}Bu), 2.60—3.00 (4H, m, SC$\underline{\mathrm{H}}_2$CH$_2$C$\underline{\mathrm{H}}_2$S), 3.58 (2H, d, J = 6 Hz, CH$_2$OSi), 4.00 (1H, t, J = 7 Hz, SCHS), 4.77—5.90 (3H, m, CH=CH$_2$), 9.25—10.00 (1H, br s, CO$_2$H, exchanged with D$_2$O). High-MS for $C_{18}H_{34}O_3SiS_2$ (M$^+$): Calcd *m/z* 390.1716. Found: 390.1654.

(3*S*,4*R*)-*N*-[2-(3-Indolyl)ethyl]-3-(propane-1,3-dithio)ethyl-4-*tert*-butyldimethylsilyloxymethyl-5-hexenamide (23) and (3*S*,4*S*)-*N*-[2-(3-Indolyl)ethyl]-3-(propane-1,3-dithio)ethyl-4-*tert*-butyldimethylsilyloxymethyl-5-hexenamide (24)——A solution of methyl chloroformate (11.8 mg, 0.125 mmol) in dichloromethane (1 ml) was added dropwise to an ice-cooled solution of the carboxylic acid (**21**) (44.3 mg, 0.114 mmol) and triethylamine (14.9 mg, 0.148 mmol) in dichloromethane (1 ml) at 0 °C and the mixture was stirred for 4 h at room temperature. The reaction mixture was extracted with chloroform. The extract was washed with brine, dried over magnesium sulfate, and then evaporated to give the crude mixed anhydride (**22**) (73.6 mg) as a yellow crystalline solid. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1823, 1764 (CO$_2$CO).

The above mixed anhydride (**22**) was dissolved in dichloromethane (5 ml), and tryptamine (21.9 mg, 0.137 mmol) was added. The mixture was stirred for 50 min and the solvent was evaporated off to leave a residue, which was purified by column chromatography on silica gel. The first elution with 30% ethyl acetate–hexane gave the desired secondary amide (**23**) (26.2 mg, 43.7%) as a pale yellow syrup. $[\alpha]_D^{26}$ −1.7° (c = 0.117, CHCl$_3$). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3478 (ArNH), 1661 (CONH). ^{1}H-NMR (CDCl$_3$) δ: 0.07 (6H, s, SiMe$_2$), 0.90 (9H, s, Si^{t}Bu), 2.60—3.13 (4H, m,

$SC\underline{H}_2CH_2C\underline{H}_2S$), 3.57 (2H, d, $J=6$ Hz, CH_2OSi), 4.03 (1H, t, $J=7$ Hz,SCHS), 4.70—5.92 (3H, m, $CH=CH_2$), 6.78—7.57 (4H, m, ArH), 8.10—8.37 (1H, br s, ArNH, exchanged with D_2O). High-MS for $C_{28}H_{44}O_2S_2Si$ (M^+): Calcd *m/z* 532.2613. Found: 532.2631. Further elution with the same solvent afforded the undesired secondary amide (**24**) 22.5 mg, 37.1%) as a pale yellow syrup. $[\alpha]_D^{26}$ $-5.0°$ ($c=0.159$, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3478 (ArNH), 1661 (CONH). ^1H-NMR ($CDCl_3$) δ: 0.06 (6H, s, $SiMe_2$), 0.88 (9H s, Si^tBu), 2.75—3.12 (4H, m, $SC\underline{H}_2CH_2C\underline{H}_2S$), 3.57 (2H, d, $J=6$ Hz, CH_2OSi), 4.01 (1H, t, $J=7$ Hz, SCHS), 6.73—7.55 (4H, m, ArH), 7.85—8.17 (1H, br s, ArNH, exchanged with D_2O). High-MS for $C_{28}H_{44}N_2O_2S_2Si$ (M^+): Calcd *m/z* 532.2613. Found: 532.2658.

(1′*S*,2*R*,12b*R*) and (1′*S*,2*R*,12b*S*)-2-(1-Hydroxymethyl-prop-2-enyl)-1,2,3,4,6,7,12,12b-octahydro-4-oxoindolo-[2,3-*a*]-quinolizine (25)——Methyl iodide (0.5 ml) and water (0.15 ml) were added to a stirred solution of the secondary amide (**23**) (36.2 mg, 0.0680 mmol) in acetonitrile (1 ml). The reaction mixture was stirred for 55 h at room temperature and then heated for an additional 14 h at 90 °C. The solvent was evaporated off to leave a residue, which was basified with 10% aqueous ammonia and then extracted with chloroform. The extract was washed with brine, dried over magnesium sulfate, and then concentrated. The crude product was purified by preparative TLC on silica gel developed with chloroform–methanol (9 : 1, v/v) to provide the lactam (**25**) (13.6 mg, 64.5%) as a pale yellow syrup. $[\alpha]_D^{25}$ $-16.2°$ ($c=0.037$, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3466 (ArNH), 3400—3200 (OH), 1627 ($CON\langle$). ^1H-NMR ($CDCl_3$) δ: 3.57 (2H, m, $C\underline{H}_2OH$), 4.57—5.63 (3H, m, $CH=CH_2$), 6.80—7.37 (4H, m, ArH), 8.40—8.57 (1H, br s, ArNH, exchanged with D_2O). High-MS for $C_{19}H_{22}N_2O_2$ (M^+): Calcd *m/z* 310.1680. Found: 310.1637.

(−)-Antirhine (5) and (−)-C_3-*epi*-Antirhine (26)——A solution of the lactam (**25**) (15.7 mg, 0.0506 mmol) in THF (0.8 ml) was added dropwise to a suspension of lithium aluminum hydride (13.4 mg, 0.354 mmol) in THF (1 ml) at 0 °C and the mixture was refluxed for 3 h under nitrogen. The mixture was cooled to 0 °C, quenched with brine, and then extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and then evaporated. The crude product was purified by preparative TLC on silica gel developed with chloroform–methanol (85 : 15, v/v) to furnish (−)-antirhine (**5**) (7.6 mg, 50.6%) and (−)-C_3-*epi*-antirhine (**26**) (3.4 mg, 22.6%) as a pale yellow solid, respectively. **5**: *Rf*=0.37 (chloroform–methanol (85 : 15, v/v). mp 112—114 °C (chloroform–ether), (lit.[10] 112—114 °C (chloroform)). $[\alpha]_D^{25}$ $-1.9°$ ($c=0.076$, $CHCl_3$), (lit.[10] $-2°$ ($c=0.23$, $CHCl_3$)), High-MS for $C_{19}H_{24}N_2O$ (M^+): Calcd *m/z* 296.1887. Found: 296.1860. The IR, ^1H-NMR and TLC behavior were identical with those of natural antirhine provided by Professor S. Sakai and Professor S. Takano. **26**: *Rf*=0.32 (chloroform–methanol (85 : 15, v/v)). $[\alpha]_D^{25}$ $-14.9°$ ($c=0.034$, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3464 (ArNH), 3400—3200 (OH). ^1H-NMR ($CDCl_3$) δ: 3.53 (1H, dd, $J=11$, 6 Hz, $C\underline{H}_2OH$), 3.66 (1H, dd, $J=11$, 5 Hz, $C\underline{H}_2OH$), 5.07 (1H, dd, $J=16$, 2 Hz, $CH=C\underline{H}_2$), 5.13 (1H, dd, $J=10$, 2 Hz, $CH=C\underline{H}_2$), 5.61 (1H, ddd, $J=16$, 10, 10 Hz, $C\underline{H}=CH_2$), 6.97—7.42 (4H, m, ArH), 7.73—8.11 (1H, br s, ArNH, exchanged with D_2O). High-MS for $C_{19}H_{24}N_2O$ (M^+): Calcd *m/z* 296.1887. Found: 296.1863.

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21) (−)-Antirhine (**5**); IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1}: 3470 (ArNH), 3400—3150 (OH). ^{1}H-NMR (CDCl$_3$) δ: 3.58 (1H, dd, $J=11$, 6 Hz, C$\underline{\text{H}}_2$OH), 3.64 (1H, dd, $J=11$, 5 Hz, C$\underline{\text{H}}_2$OH), 5.03 (1H, dd, $J=16$, 2 Hz, CH=C$\underline{\text{H}}_2$), 5.10 (1H, dd, $J=10$, 2 Hz, CH=C$\underline{\text{H}}_2$), 5.49 (1H, ddd, $J=16$, 10, 10 Hz, C$\underline{\text{H}}$=CH$_2$), 6.98—7.42 (4H, m, ArNH), 8.43—8.96 (1H, br s, ArNH).