trans-6-Amino-Cyclohept-3-Enols, a new Designed Polyfunctionalized Chiral Building Block for the Asymmetric Synthesis of 2-Substituted-4-Hydroxy Piperidines

Paolo Celestini, Bruno Danieli, Giordano Lesma,* Alessandro Sacchetti, Alessandra Silvani, Daniele Passarella, and Andrea Virdis

Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano, via Venezian 21 – 20133 Milano, Italy

giordano.lesma@unimi.it

Supporting Information Available

(1*S*,6*R*) (-)-Acetic acid 6-hydroxy-cyclohept-3-enyl ester 8.

A suspension of acetic acid 6-acetoxy-cyclohept-3-enyl ester **10** (2.65 g, 12.5 mmol) and Lipase PS (from *Pseudomonas cepacea*) (1.10 g, 30,000 μ/g) in acetone (60 mL)/phosphate buffer pH 7.2 (530 mL) was shaken at 30 °C and the pH was kept at 7.0-7.2 by adding 0.1 *M* NaOH solution with an automatic pH starter. After 53 h, the reaction was stopped by addition of AcOEt. The aqueous solution was repeatedly extracted with CH_2Cl_2, and the collected organic layers were dried over Na_2SO_4 and evaporated in vacuo affording a crude mixture which was purified by flash chromatography (FC) (SiO_2, EtOAc/*n*-hexane 1:4) to give 2.02 g (95%) of **8** (> 97% ee)[10] as an oil: R_f (AcOEt/*n*-hexane 1:3) 0.27; $[\alpha]^{24}_D$ – 51.0 (*c* 2.0, $CHCl_3$); ^{1}H NMR(300 MHz, $CDCl_3$) δ 5.74 (2H, m), 4.71 (1H, m), 3.70 (1H, tt, *J* = 9.8, 3.3 Hz), 2.45 – 2.28 (5H, m), 2.12 (1H, br s), 2.04 (3H, s), 1.88 (1H, dt, *J* = 12.4, 9.8 Hz), 1.72 (1H, br s); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.2, 128.4, 127.4, 69.4, 66.9, 46.7, 36.9, 33.6, 21.3; IR ($CHCl_3$) 1734 cm^{-1}; HRMS calcd for $C_9H_{14}O_3$: 170.0943. Found: 170.0921.

(1*S*,6*S*) (+)-Acetic acid 6-azido-cyclohept-3-enyl ester 15.

Triphenylphosphine (3.67 g, 14.0 mmol), diethyl azodicarboxylate (2.44 g, 14.0 mmol) and diphenylphosphoryl azide (3.58 g, 14.0 mmol) were added to a solution of **8** (1.19 g, 7.0 mmol) in 60 mL of dry THF and the mixture was stirred at room temperature under a N_2 atmosphere for 2 h. The suspension was passed through a Celite column using a mixture of diethyl ether-*n*-pentane (1:1) as eluant. The solvent was evaporated and the residue was purified by FC on silica gel (EtOAc/*n*-hexane 1:5) to yield pure **15** (1.05 g, 77%) as a colorless oil: R_f (AcOEt/*n*-hexane 1:5) 0.37; $[\alpha]^{24}_D$ + 57.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR(300 MHz, $CDCl_3$) δ 5.73 (2H, m), 5.06 (1H, tt, *J* = 9.2, 3.0 Hz), 3.75 (1H, tt, *J* = 8.9, 3.8 Hz), 2.56 – 2.30 (4H, m), 2.19 (1H, ddd, *J* = 13.5, 9.2, 3.8 Hz), 2.04 (1H, ddd, *J* = 13.5, 8.9, 3.0 Hz), 2.01 (3H, s); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.9, 127.9 (two carbons), 68.4, 56.1, 41.1, 33.2, 32.7, 21.1; IR ($CHCl_3$) 2098, 1734 cm^{-1}; HRMS calcd for $C_9H_{13}N_3O_2$: 195.1008. Found: 195.1013.

(1*S*,6*S*) (+)-Acetic acid 6-*tert*-butoxycarbonylamino-cyclohept-3-enyl ester 16.

To a stirred suspension of $SnCl_2$ (1.17 g, 6.2 mmol) in MeOH (100 mL) was added azidoester **15** (830 mg, 4.3 mmol). The reaction mixture was stirred at room temperature for 4 h, and freshly distilled triethylamine (12 mL) was added. The mixture was stirred for 5 min, after which time a precooled (-5 °C) solution of di-*tert*-butyl dicarbonate (1.71 g, 7.84 mmol) in THF (10 mL) was added dropwise. The mixture was stirred at room temperature for 24 h, acidified to pH 4-5 using 2N hydrochloric acid and the volatile components were removed under reduced pressure. The residue was partitioned between EtOAc (50 mL) and water (100 mL). The organic extract was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. FC of the residue (SiO_2, EtOAc/*n*-hexane 1:3) gave 740 mg (64%) of **16** as a foam: R_f (EtOAc/*n*-hexane 1:3) 0.28; $[\alpha]^{24}_D$ + 14.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR(300 MHz, $CDCl_3$, 55 °C) δ 5.73 (2H, m), 4.89 (1H, tt, *J* = 8.9, 3.8 Hz), 4.57 (1H, br s), 3.95 (1H, m), 2.45 – 2.26 (4H, m), 2.11 (1H, ddd, *J* = 13.5, 7.2, 3.8 Hz), 1.99 (3H, s), 1.98 (1H, ddd, *J* = 13.5, 8.9, 3.8 Hz), 1.43 (9H, s); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.0, 154.8, 129.0, 127.9, 79.2, 68.3, 45.7, 41.9, 33.4 (two carbons), 28.3, 21.0; IR ($CHCl_3$) 3384, 1735, 1697 cm^{-1}; HRMS calcd for $C_{14}H_{23}NO_4$: 269.1627. Found: 269.1638.

(1*S*,6*S*) (+)-(6-Hydroxy-cyclohept-3-enyl)-carbamic acid *tert*-butyl ester 17.

A mixture of **16** (455 mg, 1.69 mmol), MeOH (15 mL), and 10 N NaOH (0.29 mL, 1.7 equiv) was stirred at 45 °C for 20 h. The resulting solution was neutralized to pH 7 using 1% hydrochloric acid and the solvent was evaporated to dryness. The residue was washed with water (50 mL) and then extracted with EtOAc (60 mL, 3 times). Drying (Na_2SO_4), and solvent evaporation gave almost pure **17** (376 mg, 98%) as a foam: R_f (EtOAc/*n*-hexane 1:1) 0.32; $[\alpha]^{24}_D$ 10.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR(300 MHz, $CDCl_3$, 50 °C) δ 5.77 (2H, m), 4.43 (1H, s), 3.85 (2H, m), 2.42 – 2.18 (5H, m), 2.08 (1H, ddd, *J* = 13.0, 7.5, 4.5 Hz), 1.94 (1H, ddd, *J* = 13.0, 9.0, 3.5 Hz), 1.43 (9H, s); IR ($CHCl_3$) 3385, 1702 cm^{-1}; HRMS calcd for $C_{12}H_{21}NO_3$: 227.1521. Found: 227.1510.

(1*S*,6*S*) (+)-[6-(*tert*-Butyl-dimethyl-silanyloxy)-cyclohept-3-enyl]-carbamic acid *tert*-butyl ester 18.

(*tert*-Bu)Me_2-SiCl (705 mg, 4.68 mmol) was added dropwise to a stirred solution of **17** (532 mg, 2.34 mmol) and imidazole (478 mg, 7.03 mmol) in anhydrous DMF (16 mL) cooled to 5 °C. After stirring at 40 °C for 20 h, a saturated aqueous solution of $NaHCO_3$ (70 mL) was added, and the mixture was extracted with Et_2O (40 mL, 3 times). The combined organic extracts were washed with water, and dried (Na_2SO_4). Solvent evaporation and FC (SiO_2, EtOAc/*n*-hexane 1:5) gave 790 mg (99%) of **18** as a colorless oil: R_f (2:1 EtOAc/*n*-hexane) 0.81; $[\alpha]^{24}_D$ + 3.4 (*c* 1, $CHCl_3$); ^{1}H NMR(200 MHz, $CDCl_3$) δ 5.74 (2H, m), 4.56 (1H, br s), 3.93 (1H, br m), 3.75 (1H, m), 2.43 – 2.06 (5H, m), 2.11 (1H, ddd, *J* = 13.5, 10.0, 3.9 Hz), 1.43 (9H, s), 0.88 (9H, s), 0.06 (6H, s); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 154.9, 129.5, 128.4, 79.1, 66.2, 46.4, 46.2, 38.0, 33.1, 28.4 (three carbons), 25.7 (three carbons), 18.0, - 4.8 (two carbons); IR ($CHCl_3$) 3382, 1700 cm^{-1}; HRMS calcd for $C_{18}H_{35}NO_3Si$: 341.2386. Found: 341.2370.

(3*S*,5*R*)(-)-3-*tert*-butoxycarbonylamino-5-(*tert*-butyl-dimethyl-silanyloxy)-7-hydroxy-heptanol 19.

(1*S*,6*S*)-[6-(*tert*-Butyl-dimethyl-silanyloxy)-cyclohept-3-enyl]-carbamic acid *tert*-butyl ester (**18**) (690 mg, 2.02 mmol) was dissolved in 32 mL of a mixture of methanol and dichloromethane (1:1) at - 78 °C. Ozone (2% in O_2) was passed through the solution until the deep blue color persisted. After stirring at - 78 °C for 15 min, nitrogen was bubbled through the solution in order to remove the excess of ozone. Dimethyl sulphide (1.02 mL) and $NaBH_4$ (464 mg, 12.2 mmol) were added and the mixture was stirred at 25 °C for 30 min. Water (150 mL) was added, and the mixture was extracted with Et_2O (40 mL, three times). Drying (Na_2SO_4), solvent evaporation, and FC (SiO_2, EtOAc/*n*-hexane 1:1) gave 548 mg (72%) of **19** as a colorless oil: R_f (1:1 EtOAc/*n*-hexane) 0.18; $[\alpha]^{24}_D$ - 6.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR(300 MHz, $CDCl_3$) δ 4.95 (1H, br d, *J* = 7.8 Hz), 4.07 (1H, m), 3.88 (1H, br m), 3.77 (1H, ddd, *J* = 11.2, 7.3, 4.9 Hz), 3.69 (1 H, dt, *J* = 11.2, 5.9 Hz), 3.60 (2H, dd, *J* = 7.9, 3.0 Hz), 1.88 – 1.54 (6H, m), 1.43 (9H, s), 1.40 (2H, br s), 0.87 (9H, s), 0.08 (6H, s); IR ($CHCl_3$) 3380, 1697 cm^{-1}; HRMS calcd for $C_{18}H_{39}NO_5Si$: 377.2598. Found: 377.2581.

(3*S*,5*R*)-Methanesulfonic acid 3-*tert*-butoxycarbonylamino-5-(*tert*-butyl-dimethyl-silanyloxy)-7-methanesulfonyl-oxy-heptyl ester 20.

To a dry CH_2Cl_2 solution (20 mL) of compound **19** (389 mg, 1.03 mmol) cooled to 0 °C were added dropwise triethylamine (520 mg, 5.15 mmol, 5 equiv) and mesyl chloride (354 mg, 3.09 mmol, 3 equiv). After the end of addition, the mixture was allowed to heat slowly to room temperature. After 9 h at room temperature, saturated aqueous NH_4Cl (50 mL) and H_2O (50 mL) were added, and the mixture was extracted with Et_2O (20 mL, three times). The combined organic layers were washed sequentially with water and brine, and dried over Na_2SO_4. The solvent was removed by rotary evaporation to give almost pure, crude dimesylate **20** (538 mg, 98%) as colourless oil, which was used in the next step without further purification: R_f (AcOEt/*n*-hexane 1:1) 0.21; ^{1}H NMR(200 MHz, $CDCl_3$) δ 4.69 (1H, m), 4.09 (4H, t, *J* = 6.5 Hz), 3.91 (1H, quint, *J* = 5.8 Hz), 3.62 (1H, m), 2.99 (6 H, s), 1.84 (4H, m), 1.54 (2H, t, *J* = 6.2 Hz), 1.41 (9H, s), 0.86 (9H, s), 0.04 (3H, s), 0.02 (3H, s); IR ($CHCl_3$) 3384, 1699, 1360 cm^{-1}; MS (FAB$^+$) *m/z* 534 (MH^+).

(2*S*,4*S*) (+)-4-(*tert*-Butyl-dimethyl-silanyloxy)-2-(2-methanesulfonyloxy-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester 21.

To a stirred suspension of NaH (32 mg, 1.34 mmol) in 5 mL of dry DMF at 0 °C, was added dropwise a solution of the crude dimesylate **20** (538 mg, 1.01 mmol) in 5 mL of dry DMF. After stirring for 15 min at 0 °C, the mixture was allowed to warm to room temperature and stirred for additional 6 h. Saturated aqueous NH_4Cl (100 mL) was added, and the mixture was extracted with Et_2O (25 mL, three times). The combined organic layers were washed sequentially with water and brine, and dried over Na_2SO_4. Solvent evaporation, and FC (SiO_2, EtOAc/*n*-hexane 1:3) gave 266 mg (59 %) of **21** as a colorless oil: R_f (EtOAc/*n*-hexane 1:3) 0.16; $[\alpha]^{24}_D$ + 13.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR(300 MHz, $CDCl_3$) δ 4.36 (1H, br quint, *J* = 6.5 Hz), 4.18 (2H, m), 4.10 (1H, br quint, *J* = 3.0 Hz), 3.87 (1H, br d, *J* = 12.9 Hz), 3.16 (1H, ddd, *J* = 12.9, 12.0, 3.9 Hz), 2.99 (3H, s), 2.50 (1H, ddt, *J* = 14.9, 10.7, 6.5 Hz), 2.03 (1H, ddt, *J* = 14.9, 6.5, 4.8 Hz), 1.77 (1H, ddd, *J* = 14.4, 6.5, 3.0 Hz), 1.68 – 1.53 (3H, m), 1.45 (9H, s), 1.40 (2H, br s), 0.89 (9H, s), 0.08 (6H, s); ^{13}C NMR (75.4

MHz, $CDCl_3$) δ 154.9, 83.5, 68.8, 64.1, 51.9, 43.1, 39.7, 34.8, 34.4, 29.2, 28.3, 25.6, 24.9, - 4.4; IR ($CHCl_3$) 1700, 1360 cm^{-1}; HRMS calcd for $C_{19}H_{39}NO_6SiS$: 437.1328. Found: 437.1334.

(1*S*,6*R*) (-)-Acetic acid-6-(*tert*-butyl-dimethyl-silanyloxy)-cyclohept-3-enyl ester 22.

The title compound was prepared according to the method outlined for **18**, whereby **8** (1,29 g, 7.05 mmol), imidazole (1.44 g, 21.15 mmol) and (*tert*-Bu)Me_2-SiCl (2.15 g, 14.1 mmol) were reacted under the conditions described (except reaction quenched at r.t. after 120 min). Purification was accomplished by FC (SiO_2, EtOAc/*n*-hexane 1:3) to yield **22** (1.85 g, 92 %) as a very pale yellow oil: R_f (1:2 EtOAc/*n*-hexane) 0.56; $[\alpha]^{24}_D$ – 6.2 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (2H, m), 4.65 (1H, m), 3.61 (1H, m), 2.38 – 2.22 (5H, m), 2.01 (3H, s), 1.82 (1H, dt, *J* = 13.5, 10.5 Hz), 0.89 (9H, s), 0.07 (6H, s); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.0, 128.6, 127.1, 69.4, 67.7, 47.8, 37.8, 33.6, 25.7, 21.3, - 4.8 (two carbons); IR ($CHCl_3$) 1733 cm^{-1}; HRMS calcd for $C_{15}H_{28}O_3Si$: 284.1808. Found: 284.1817.

(1*S*,6*R*) (+)-6-(*tert*-Butyl-dimethyl-silanyloxy)-cyclohept-3-enol 14.

The title compound was prepared according to the method outlined for **17**, whereby reaction of **22** (1,85 g, 6.50 mmol) with NaOH and workup under the conditions described, followed by FC purification (SiO_2, EtOAc/*n*-hexane 1:3) yielded **14** (1.50 g, 95 %) as an oil: R_f (1:3 EtOAc/*n*-hexane) 0.32; $[\alpha]^{24}_D$ + 6.1 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (2H, m), 3.81 (1H, tt, *J* = 7.9, 3.4 Hz), 3.75 (1H, tt, *J* = 7.9, 3.4 Hz), 2.48 – 2.22 (5H, m), 2.10 (1H, br, dt, *J* = 13.4, 3.4 Hz), 2.01 (1H, dt, *J* = 13.4, 7.9 Hz), 0.85 (9H, s), 0.01 (6H, s); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 128.5, 128.2, 68.4, 67.5, 48.3, 36.8, 36.6, 25.8, 21.3, -4.9 (two carbons); HRMS calcd for $C_{13}H_{26}O_2Si$: 242.1702. Found: 242.1712.

(1*R*,6*S*) (-)-(6-Azido-cyclohept-3-enyloxy)-*tert*-butyl-dimethyl-silane 23.

The title compound was prepared according to the method outlined for **15**. Reaction of **14** (667 mg, 2.75 mmol) with diphenylphosphoryl azide (1.95 g, 6.88 mmol), triphenylphosphine (1.82 g, 6.88 mmol), and diethyl azodicarboxylate (1.19 g, 6.88 mmol) under the conditions described (except reaction quenched after 60 min), followed by FC purification (SiO_2, CH_2Cl_2/*n*-pentane 1:5), yielded **23** (530 mg, 72 %) as an oil: R_f (1:10 EtOAc/*n*-hexane) 0.56; $[\alpha]^{24}_D$ – 46.0 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (2H, m), 4.02 (1H, tt, *J* = 7.7, 3.4 Hz), 3.78 (1H, tt, *J* = 8.3, 3.4 Hz), 2.49 – 2.21 (4H, m), 2.09 (1H, ddd, *J* = 13.4, 7.7, 3.4 Hz), 1.99 (1H, ddd, *J* = 13.4, 8.3, 3.4 Hz), 0.85 (9H, s), 0.04 (6H, s); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 128.9, 127.2, 66.2, 56.5, 45.0, 36.8, 33.2, 25.8, - 4.9 (two carbons); IR ($CHCl_3$) 2105 cm^{-1}; HRMS calcd for $C_{13}H_{25}N_3OSi$: 267.1767. Found: 267.1750.

(1*R*,6*R*) (-)-[6-(*tert*-Butyl-dimethyl-silanyloxy)-cyclohept-3-enyl]-carbamic acid *tert*-butyl ester ent-18.

The title compound was prepared according to the method outlined for **16**. Reaction of **23** (1.15 g, 4.3 mmol) with $SnCl_2$ (1.17 g, 6.2 mmol) and di-*tert*-butyl dicarbonate (1.71 g, 7.84 mmol) under the conditions described (except reaction quenched with water after 18 h), followed by FC purification (SiO_2, EtOAc/*n*-hexane 1:3) yielded **ent-18** (968 mg, 66 %) as a colorless oil: $[\alpha]^{24}_D$ - 3.2 (*c* 1, $CHCl_3$); whose ^{1}H NMR, ^{13}C NMR and MS spectral data were identical in all respects to that reported above for **18**.

(2*S*,4*S*) (+)-2-Pent-3-enyl-piperidin-4-ol 4.

To a cooled (- 78 °C) mixture of compound **21** (700 mg, 1.6 mmol) and CuI (438 mg, 2.3 mmol) in 15 mL of THF under a nitrogen atmosphere, was added (*E*)-propenylmagnesium bromide[16a] (1.45 g, 10 mmol) over a 5 min period during which the suspension turned from grey to yellow. The suspension was stirred at – 78 °C for 30 min and then at 25 °C for 5 h. Saturated NH_4Cl (10 mL) was added carefully to the reaction mixture which was then stirred at RT for 30 min; after this it was subjected to rotoevaporation. The resulting blue solution was extracted with EtOAc (50 mL, three times), and the combined extracts where dried (Na_2SO_4), filtered, evaporated and the residue was dissolved in 3 N HCl in MeOH (50 mL). After 12 h, the solvent was removed under reduced pressure and the residue was partitioned between dichloromethane (50 mL) and saturated $NaHCO_3$ solution (70 mL). The phases were separated, and the organic phase was dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the residue by FC (SiO_2, EtOAc/MeOH 4:1) afforded pure (2*S*,4*S*) (+)-2-Pent-3-enyl-piperidin-4-ol **(4)** (146 mg, 54%) as a colorless oil: $[\alpha]^{24}_D$ + 6.9 (*c* 2.0, MeOH); whose ^{1}H NMR, ^{13}C NMR and MS spectral data were identical in all respects to the reported ones.[6]

(2*R*,4*S*) (+)-4-(*tert*-Butyl-dimethyl-silanyloxy)-2-vinyl-piperidine-1-carboxylic acid *tert*-butyl ester 24.

To a cooled (0 °C) suspension of 2-nitrophenyl selenocyanate (565 mg, 2.4 mmol) in absolute ethanol (12 mL), sodium borohydride (101 mg, 2.65 mmol) was added in small portions, under stirring (Caution! reduction of the selenocyanate is exothermic and vigorous hydrogen evolution occurs). The mesylate **21** (1.05 g, 2.4 mmol) in 5 mL of

dry ethanol was added dropwise to the resulting dark red solution and the mixture was stirred at RT for 18 h. Tetrahydrofuran (8 mL) was added; after cooling at 0 °C, 30% hydrogen peroxide (2.1 mL, 2.4 mmol) was added dropwise over a period of 30 min. The ice bath was removed and the solution stirred for an additional 4 h. The mixture was diluted with water and extracted with EtOAc. The organic layer was washed with aqueous sodium carbonate and brine, dried (Na_2SO_4), and concentrated under reduced pressure to give a dark orange residue. FC (SiO_2, EtOAc/*n*-hexane 1:6) of the residue yielded 622 mg (76 %) of **24** as an oil: R_f (EtOAc/*n*-hexane 1:2) 0.58; ; $[\alpha]^{24}_D$ + 4.9 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.12 (1H, ddd, *J* = 16.5, 10.0, 6.3 Hz), 4.97 (1H, dt, *J* = 16.5, 1.5 Hz), 4.94 (1H, dt, *J* = 10.0, 1.8 Hz), 4.64 (1H, m), 4.09 (1H, quint, *J* = 3.3 Hz), 3.81 (1H, br, ddd, *J* = 13.2, 5.0, 3.8 Hz), 3.26 (1H, ddd, *J* = 13.2, 11.9, 3.9 Hz), 1.83 (1H, ddd, *J* = 14.0, 10.0, 3.3 Hz), 1.72 (1H, ddt, *J* = 14.0, 3.3, 1.5 Hz), 1.65-1.50 (2H, m), 1.38 (9H, s), 0.82 (9H, s), 0.04 (6H, s); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 155.3, 139.0, 112.6, 79.3, 64.7, 52.2, 37.1, 34.1, 32.7, 28.4, 25.7, - 5.0; IR ($CHCl_3$) 1700 cm^{-1}; HRMS calcd for $C_{18}H_{35}NO_3Si$: 341.2386. Found: 341.2399.

(2*R*,4*S*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-2-formyl-piperidine-1-carboxylic acid *tert*-butyl ester 25.

Ozone was bubbled through a solution of **24** (447 mg, 1.31 mmol) in a mixture of methanol and dichloromethane (1:1) (200 mL) at –78 °C until the color of the solution remained light blue. Dimethyl sulfide (10 mL) was added, and the solution was slowly warmed to rt. The mixture was diluted with dichloromethane (100 mL), washed with brine, and dried (Na_2SO_4). Concentration *in vacuo* gave a residue which was purified by FC (SiO_2, EtOAc/*n*-hexane 1:6) to give crude aldehyde **25** as an oil (350 mg, 78%) which was not further purified but used directly in the next step: R_f (EtOAc/*n*-hexane 1:2) 0.63; IR ($CHCl_3$) 1700, 1740 cm^{-1}.

(2*R*,4*S*) (+)-*cis*-4-Hydroxy-2-pipecolic acid 1.

To a solution of the above crude aldehyde **25** (309 mg, 0.9 mmol) in *t*-BuOH/phosphate buffer (pH 7.2) (2:1, 10.2 mL) was added dropwise a 1 M aqueous solution of $KMnO_4$ (5.13 mL, 5.13 mmol). After stirring at room temperature for 1 h, aqueous $NaHSO_3$ (5%) was added, and the resulting solution was acidified (pH 4) with 1 M HCl and extracted with EtOAc (10 mL, three times). The combined organic extracts were concentrated, the residue was dissolved in 3 N HCl in MeOH (30 mL) and the solution refluxed overnight. After 12 h, the solution was made neutral with 1N aqueous KOH and concentrated to a final volume of about 0.5 mL. This solution was acidified (pH 4) with 0.1N HCl and applied to a column filled with Dowex 50 W (H^+) resin. The column was washed with water and then eluted with 0.5 M aqueous pyridine. Fractions that gave the positive ninhydrin test were pooled and freeze-dried, affording (2*R*,4*S*) (+)-**1** (103 mg, 79%) as a white solid, which was recrystallized from hot 25% water in EtOH: mp 274-275 °C; $[\alpha]^{24}_D$ + 21.3 (*c* 0.5, H_2O); {lit[2b] mp 273-275 °C; $[\alpha]^{24}_D$ – 23.5 (*c* 1, H_2O) for the enantiomer}, whose ^{1}H NMR, ^{13}C NMR and MS spectral data were identical in all respects to the reported ones.[8c,d]

(2*R*,4*S*) (+)-2-Penta-1,3-dienyl-piperidin-4-ol 3.

To a stirred suspension of crotyltriphenylphosphonium bromide (397 mg, 1.0 mmol) in THF (3 mL) at –30 °C was added dropwise a 1.2 M solution of BuLi in hexane (0.83 mL, 1.0 mmol). The mixture was stirred at –30 °C for 1.5 h followed by dropwise addition of the crude aldehyde **25** (281 mg, 0.82 mmol) in THF (1 mL) over 5 min. The stirring was continued for 1 h at –30 °C, and the solution was then allowed to warm to room temperature. The mixture was carefully quenched with ice-water (15 mL), and extracted with Et_2O (5 mL, three times). The combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated to a colorless oil, which was dissolved in benzene (50 mL), and I_2 (ca. 2 mg) was added. After the solution was irradiated through Pyrex with a 100-W high-pressure Hg lamp for 40 min, it was washed with 5% aqueous $Na_2S_2O_3$ (5 mL) and water, dried (Na_2SO_4), and concentrated. The residue was dissolved in 3 N HCl in MeOH (10 mL). After 12 h, the solvent was removed under reduced pressure and the residue was partitioned between dichloromethane (15 mL) and saturated $NaHCO_3$ solution (15 mL). The phases were separated, and the organic phase was dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the residue by FC (SiO_2, EtOAc/MeOH 4:1) afforded isomerically pure (2*R*,4*S*) (+)-2-Penta-1,3-dienyl-piperidin-4-ol (**3**) (88 mg, 64%) as a white solid, which was recrystallized from Et_2O: mp 67 °C; $[\alpha]^{24}_D$ + 37.8 (*c* 1, $CHCl_3$); { lit.[5] mp for the enantiomer, 67-68 °C; $[\alpha]^{25}_D$ + 39 (*c* 1.0, $CHCl_3$) }, whose ^{1}H NMR, ^{13}C NMR and MS spectral data were identical in all respects to the reported ones.[5]